Closed Relation Between Carotid and Ascending Aortic Atherosclerosis in Cardiac Patients

Ioannis E. Kallikazaros, MD; Costas P. Tsioufis, MD; Christodoulos I. Stefanadis, MD; Christos E. Pitsavos, MD; Pavlos K. Toutouzas, MD

Background—Carotid atherosclerosis and aortic atherosclerosis are both associated with coronary artery disease and cerebral thromboembolism. However, the relationship between asymptomatic carotid and aortic atherosclerosis is not well known.

Methods and Results—Sixty-two consecutive cardiac patients (mean age 57 years) without a history of atherosclerotic cardiovascular disease who were referred for transesophageal echocardiography were included. By means of a high-resolution ultrasound technique, normal carotid arteries were found in 12 patients (19.4%), whereas 15 patients (24.2%) had increased intima-media thickness, and the remaining 35 patients (56.5%) had atherosclerotic plaques (intima-media thickness ≥1.3 mm). Transesophageal echocardiography characterized ascending aortic intimal morphology as normal in 1 patient (1.6%), as thickening in 22 patients (35.5%), and as atherosclerotic plaques in 39 patients (62.9%). Patients with both carotid and aortic plaques were older compared with patients without plaques; also, a higher percentage of patients with carotid and aortic plaques suffered from hypertension and diabetes mellitus compared with patients without plaques (P<0.001). The incidence of carotid plaques was 74.3% (29 of 39 patients) in the subgroup with aortic plaques; there was a stepwise increase in the percentage of patients with carotid plaques among the patients with increasing grades of aortic atherosclerosis. Furthermore, the incidence of ascending aortic plaques was 82.8% (29 of 35 patients) in the subgroup with carotid plaques. Regression analysis revealed that age and carotid plaques were independently related to the presence of aortic plaques. In the entire study population, the presence of carotid plaques had a high positive predictive value (83%), an acceptable sensitivity (75%) and specificity (74%), and a relatively low negative predictive value (63%) for the presence of aortic plaques.

Conclusions—In cardiac patients without clinical evidence of atherosclerotic cardiovascular disease, a high prevalence of combined aortic and carotid plaques were detected. The presence of carotid plaque reflects the presence of aortic plaque, whereas the absence of carotid plaque may not reflect the absence of aortic plaque. (Circulation. 2000;102[suppl III]:III-263-III-268.)

Key Words: atherosclerosis ■ carotid arteries ■ aorta ■ ultrasonics

Epidemiological studies have documented that individuals with clinical cardiovascular disease related to one specific peripheral vascular bed are at a higher risk of clinical disease caused by atherosclerosis at another site, such as the heart or brain.1 Furthermore, because of the systemic nature of atherosclerosis, the presence of subclinical markers in subjects without evidence of clinical cardiovascular disease is associated with a significant increased risk of incident coronary heart disease for both men and women.2 Accordingly, there is a growing belief that carotid intima-media thickness (IMT), being evaluated by using high-resolution ultrasonography, can be regarded as an indicator of generalized atherosclerosis and that it may be used as an intermediate end point in observational studies or as a suitable alternative for cardiovascular morbidity and mortality.3,4 Similarly, an atherosclerotic ascending aorta, detected by multiplane transesophageal echocardiography (TEE), represents a potential source of emboli or may be a marker for the presence of coronary artery disease (CAD).5,6 However, the precise relationship between the extent of asymptomatic atherosclerosis located on the carotid artery and on the ascending aorta has not been well evaluated. For this purpose, we studied, by carotid artery ultrasonography, the potential role of carotid atherosclerotic plaque in identifying the presence of aortic atherosclerotic plaques in patients who had been referred for evaluation by TEE.

Methods

Study Population

Eighty-one patients referred for TEE to the echocardiographic laboratory of our clinic during a 3-month period were entered in a prospective study of carotid artery wall disease approved by the local
Assessment of Risk Factor Variables

The risk factor variables evaluated in the present 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 one 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 a 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 as present 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 a 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 the carotid arteries was assessed by duplex ultrasound scanning with use of an ultrasonic device equipped with an 8-MHz high-resolution annular array scanner (2000 II s.a., Biomed, Inc) with a nominal axial resolution of 0.3 mm and a 30-frame/s acquisition. The ultrasonographic examinations were performed by 2 qualified physicians certified by the Division of Vascular Ultrasound Research of the Wake Forest University Medical Center, Winston Salem, NC. The technique for carotid artery ultrasound scanning was based on the protocol followed by the European Lacidipine Atherosclerosis (ELSA) Study. In brief, with the subject in the supine position, a careful search was performed for all interfaces of up to 12 different sites (right and left, near and far walls, distal common, bifurcation, and proximal internal carotid artery). When an optimal longitudinal image was obtained, it was frozen on the R wave of the ECG and stored on S-VHS videotape. This procedure was repeated 3 times for each site examined. The quantitative measurements of IMT were performed offline; from the videotape, the frozen images were digitized and displayed on the screen of a personal computer by using additional dedicated software. The average of the 3 frozen images at each site was calculated. For each individual, the carotid IMT was determined as the overall mean maximum IMT (T max). Accord-

Evaluation of Aortic Atherosclerosis

TEE examinations were performed in all patients by use of an HP Sonos 2500 (Hewlett-Packard Co) imager equipped with a 3.5/7-

Results

The demographic and clinical characteristics of the entire study population, as well as of the subgroups with carotid and aortic atherosclerotic plaques, are presented in Table 1. These subgroups have a common incidence of the well-known cardiovascular risk factors.

Carotid Artery Duplex Ultrasonography Data

Carotid artery thickening or atherosclerotic plaque was present in 50 patients (80.6%), whereas 12 patients (19.4%) had normal left and right carotid arteries. Furthermore, 15 patients (24.2%) were classified into category II; 29 patients (46.8%), into category III; and the remaining 6 patients (9.7%), into the category IV. Regarding the location of atherosclerotic plaque in the carotid tree, the bulb was the most common site (in 27 lesions) and, subsequently, the internal carotid artery (in 18 lesions) and the common carotid artery (in 11 lesions). Furthermore, carotid artery plaques were found to be equally distributed between the right and left carotid arteries.

Patients with carotid atherosclerotic plaques were older compared with patients with normal or thickening carotid mobile or ulcerated plaque. We defined as carotid atherosclerotic plaque the latter 2 categories.

The readers of the ultrasound images from videotape were unaware of the case status of the subject. Reproducibility of IMT measurements was evaluated in 10 randomly selected subjects who were invited to undergo a repeated carotid examination by both physicians 10 days after the original assessment. The coefficients of variation for intrareader and inter-reader variability for repeated examinations and measurements of IMT were 5.1% and 7.7%, respectively.

Statistical Analysis

To detect statistically significant relationships between categorical variables, χ2 tests were used. An independent-sample t test was used to determine the statistically significant difference between groups. A value of P<0.05 was considered statistically significant.

Stepwise multiple logistic regression analysis was used to detect statistically significant associations between a dichotomous dependent variable and a number of independent variables. Carotid artery ultrasonographic data and corresponding transesophageal data were compiled on a 2×2 contingency table to allow calculation of sensitivity and specificity as well as predictive values.

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arteries (62.5 ± 8 versus 48.7 ± 11 years, *P* < 0.0001); also, a higher percentage of patients with carotid atherosclerotic plaques suffered from hypertension and diabetes mellitus compared with patients without plaques (43% and 28% versus 17% and 4%, respectively; *P* < 0.05 for both cases). However, multiple logistic regression analysis revealed that only the age was independently associated with the presence of carotid atherosclerotic plaque (Table 2).

### Aortic Findings

TEE characterized thoracic aortic intimal morphology as grade I in 1 patient (1.6%), grade II in 22 patients (35.5%), grade III in 32 patients (51.6%), and grade IV in 7 patients (11.3%). Aortic atherosclerotic plaques were found in 39 patients (62.9%).

Patients with aortic atherosclerotic plaques were older compared with patients with normal or thickening ascending aorta (63.1 ± 8 versus 46.2 ± 11 years, *P* < 0.0001); also, as in the case of carotid atherosclerosis, a higher percentage of patients with aortic atherosclerotic plaques suffered from hypertension and diabetes mellitus compared with patients without aortic plaques (41% and 26% versus 13% and 4%, respectively; *P* < 0.05 for both cases).

### Correlation Between Carotid and Aortic Atherosclerosis

The incidence of carotid atherosclerotic plaques was 56.4% (35 of 62 patients) in the entire population and 74.3% (29 of 39 patients) in the subgroup with aortic atherosclerotic plaques.

Regarding the distribution of carotid atherosclerotic plaques in the groups with different grades of ascending aorta atherosclerosis, there was a stepwise increase in the percentage of patients with carotid plaques among the patients with increasing grades of aortic atherosclerosis because carotid plaques were present in 0% (0 of 1 patient), 27.2% (6 of 22 patients), 71.8% (23 of 32 patients), and 85.7% (6 of 7 patients) of the groups of patients with grade I, II, III, and IV aortic atherosclerosis, respectively (Figure 1).

The incidence of ascending aortic atherosclerotic plaque was 62.9% (39 of 62 patients) in the entire population and 82.8% (29 of 35 patients) in the subgroup with carotid atherosclerotic plaques. Furthermore, there was a stepwise increase in the percentage of patients with aortic atherosclerotic plaques among the patients with increasing degrees of carotid atherosclerosis. Aortic atherosclerotic plaques were present in 33.3% (4 of 12 patients), 40% (6 of 15 patients), 79.3% (23 of 29 patients), and 100% (6 of 6 patients) of the group of patients with category I, II, III, and IV carotid atherosclerosis, respectively (Figure 2). Forward stepwise logistic regression analysis was applied to identify factors that were independently associated with the presence of aortic atherosclerotic plaques. This analysis revealed that age and carotid atherosclerotic plaques were independently related to the presence of aortic atherosclerotic plaques in the entire study population (Table 3).

In the entire study population, the presence of carotid atherosclerotic plaque has a high positive predictive value (83%), an acceptable sensitivity (75%) and specificity (74%), and a relatively low negative predictive value (63%) for the presence of aortic atherosclerotic plaque.

### Discussion

In the present study, we evaluated the relationship between atherosclerosis in the carotid arteries and in the ascending aorta in patients without clinical evidence of atherosclerotic cardiovascular disease who were referred for evaluation by TEE. Our main finding was that there is a close association between asymptomatic carotid and aortic atherosclerotic plaque. The prevalence of aortic plaque increased as the degree of carotid atherosclerosis increased, suggesting that in cardiac patients, the ascending aorta was the part most exposed to early asymptomatic atherosclerosis.

Atherosclerosis is a generalized process that may involve the entire vasculature. Although it mainly manifests itself in medium-sized vessels, it is also present in the great vessels, such as the thoracic or abdominal aorta and the carotid artery. Autopsy and epidemiological studies have clearly demonstrated an association between carotid atherosclerosis

### TABLE 1. Clinical Characteristics of Entire Study Population and Subgroups With Carotid and Aortic Atherosclerotic Plaques

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire Population (n=62)</th>
<th>Patients With Carotid Plaques (n=35)</th>
<th>Patients With Aortic Plaques (n=39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±12</td>
<td>62±8</td>
<td>63±8</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female), n/n</td>
<td>38/24</td>
<td>23/12</td>
<td>25/14</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>25 (40)</td>
<td>15 (43)</td>
<td>16 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertensives, n (%)</td>
<td>19 (30)</td>
<td>15 (43)</td>
<td>16 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>11 (17)</td>
<td>10 (28)</td>
<td>10 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>26 (42)</td>
<td>17 (48)</td>
<td>17 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive family history, n (%)</td>
<td>17 (27)</td>
<td>13 (37)</td>
<td>14 (36)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### TABLE 2. Stepwise Multiple Logistic Regression Coefficients for Relationship Between 7 Variables and Carotid Atherosclerotic Plaques in Entire Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient b</th>
<th>Wald</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.12</td>
<td>8.18</td>
<td>0.004</td>
</tr>
<tr>
<td>Constant</td>
<td>-7.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The variables male sex, 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).
and aortic atherosclerosis with CAD.\textsuperscript{3,13–15} Noninvasive measurements of carotid IMT by using high-resolution B-mode ultrasound scan have been suggested as a surrogate marker for coronary atherosclerosis for use in clinical trials.\textsuperscript{2,3,9–11,14} Recently, the Atherosclerosis Risk in Communities study\textsuperscript{15} and the Rotterdam study\textsuperscript{3} reported that carotid IMT is a noninvasive predictor of future cardiovascular events. We have recently reported that in patients being evaluated for chest pain, the presence of carotid disease is significantly related to the presence of severe CAD.\textsuperscript{8}

In a similar way, previous roentgenographic studies have attempted to correlate the presence of atherosclerotic aortic plaque with CAD.\textsuperscript{16} However, the limited resolution of x-ray studies for aortic plaque resulted in the inability to detect plaque consistently. TEE has become a unique ultrasound tool that allows improved visualization of the aorta because of its proximity to the esophagus. Increased thickness and complexity of aortic plaques as visualized by TEE have been recently associated with a high incidence of coronary events.\textsuperscript{6,17–19}

**Figure 1.** Distribution of percentage of patients with carotid atherosclerotic plaques according to grade of ascending aortic atherosclerosis.

**Figure 2.** Distribution of percentage of patients with aortic atherosclerotic plaques according to degree of carotid artery atherosclerosis.
Apart from the well-defined association between carotid or aortic atherosclerosis with CAD, the extracranial carotid artery is one of the main sources of cerebral thromboembolism in a significant number of patients. After cardiogenic embolism, carotid bifurcation is the second cause of stroke or transient ischemic attack. However, the atherosclerotic thoracic aorta had not been considered to be an important or common cause of cerebral and peripheral embolism until recently. Davila-Roman et al. in 1993 reported that cardiac surgical patients with atherosclerosis of the ascending aorta have a significantly higher incidence of previous cerebrovascular events, independent of other demographic and clinical data. Recently, the same investigators in a prospective, long-term, follow-up study confirmed that atherosclerosis of the ascending aorta is an independent predictor of long-term neurological events and of all-cause mortality.

According to the above, carotid atherosclerosis and aortic atherosclerosis are both important, mainly because of their relation to cerebrovascular ischemic disease and to coronary artery atherosclerosis. However, possible additional associations between carotid and aortic atherosclerotic plaque have not been well addressed. To investigate this issue further, we extended our attention to the exact relationship between atherosclerosis in the carotid tree and in the ascending aorta by using noninvasive methodology. We found that the presence of asymptomatic carotid atherosclerotic plaques could indicate the presence of aortic atherosclerotic plaques in cardiac patients undergoing TEE, whereas the absence of carotid plaques may not reflect the absence of aortic plaques. The comparison of plaque prevalence between the carotid and ascending aortas is of great interest because so few data are available in this setting. Moreover, less information, often conflicting, is available regarding unselected middle-aged subjects, those who are the most affected by the atherosclerotic process. Thus, in 1985, Bots et al. reported that among elderly women with roentgenographically determined atherosclerotic plaque in the abdominal aorta, the ultrasonographically determined IMT of the distal common carotid artery was increased. In contrast, Giral et al. did not find any relationship between carotid and aortic plaque by assessing hypercholesterolemic men.

The precise mechanism for the association between carotid and aortic plaque is unclear. Aortic and carotid atherosclerosis maybe tightly related because both are epiphenomena; however, there are different sequences depending on geometry, on artery size, and on different reactions to different risk factors. A spatial variability of hemodynamic factors along the arterial tree may play a major role in the focal preferential distribution of atherosclerosis in human vessels.

Although the correlation between the well-defined cardiovascular risk factors and the presence of carotid and/or aortic atherosclerosis was not the primary objective of the present study, some interesting relations emerged from that analysis. A higher percentage of patients with hypertension and diabetes mellitus were found in the subgroups with carotid and aortic atherosclerotic plaque compared with subgroups with no plaque. In agreement, the role of hypertension as the most powerful risk factor for stroke and the reduction of this risk with adequate therapy have been well documented in numerous studies. Similarly, but to a lesser extent, diabetes mellitus has been associated with an increased risk of stroke and a poor prognosis after stroke. However, in our population, by applying multiple regression analysis, it was revealed that only age was significantly related to carotid and aortic atherosclerosis. Our finding is in agreement with previous studies. Aging influences the pathogenesis of atherosclerosis in terms of physiological vascular changes and of increasing exposure to traditional risk factors. It is suggested that the other common cardiovascular risk factors lose some of their importance as age increases.

The pathway from risk factors to clinical disease is probably through the development of a subclinical state. Therefore, the identification of these subclinical states may provide a very important marker for the effects of risk factors on the cardiovascular system among relatively asymptomatic individuals. It is possible that the risk of subclinical disease is a function of both current exposure and duration of exposure to a specific level or extent of a risk factor. The measurement of subclinical disease by tests may be used to identify higher-risk individuals, especially middle-aged or older subjects. Accordingly, our findings may have some useful clinical implications. The high incidence of combined asymptomatic carotid and aortic plaques emphasize that many middle-aged subjects have subclinical disease that may substantially increase the risk of clinical cardiovascular disease. Until now, there has not been a noninvasive method that could be used as a first-line screening test for aortic atherosclerosis status inasmuch as TEE is a moderately invasive procedure. Our findings support the view that carotid B-mode ultrasound, a noninvasive, reliable, and valid method, is of considerable interest, permitting the study of atherosclerosis in vivo during its subclinical phase because it provides predictive validity for atherosclerosis elsewhere. Such information about the asymptomatic atherosclerotic load in the carotid artery and ascending aorta may lead to further revision of the guidelines for the identification and more aggressive treatment of individuals with a higher probability of a clinical cardiovascular event.

The strength of the relationship that we found between carotid and aortic atherosclerosis may have been limited by the following factors. First, we studied a group of consecutive patients who were referred for TEE for cardiac causes. This selection bias means that our findings regarding the relation of carotid atherosclerotic plaques with aortic atherosclerosis are relevant only to this special group of patients and may not
be applicable to the general population. Second, we collected data on atherosclerosis of the ascending aorta only, not the aortic arch or the descending aorta. Thus, it is possible that the true incidence of atherosclerotic plaque in the aorta was underestimated.

In conclusion, in cardiac patients without clinical evidence of atherosclerotic cardiovascular disease, a high prevalence of combined aortic and carotid plaque was detected. The presence of carotid plaque reflects the presence of aortic plaque, whereas the absence of carotid plaque may not reflect the absence of aortic plaque. However, further work is needed to clarify the relationship between combined carotid and ascending aorta atherosclerotic load and the development of symptomatic cardiovascular disease.

References

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