Carotid Atherosclerosis as a Risk Factor for Complex Aortic Lesions in Patients With Ischemic Cerebrovascular Disease

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Aortic arch atherosclerotic lesions can cause ischemic cerebrovascular disease (ICVD). The association between carotid and aortic atherosclerosis was examined, and it was investigated whether noninvasive carotid evaluation aids in the identification of aortic lesions as potential ICVD risk. The subjects comprised 147 patients with ICVD who had undergone carotid ultrasonography and transesophageal echocardiography. Carotid and aortic arch atherosclerosis was evaluated by measuring the maximum intima-media thickness (IMT), with aortic IMT of at least 4 mm, mobile plaques and/or ulcers defined as complex aortic lesions with potential ICVD risk. Carotid IMT was linearly associated with aortic IMT (r=0.53, p<0.001), and the association was independent of traditional cardiovascular risk factors (r=0.36, p<0.001). Also, each 1 SD greater carotid IMT was associated with 4.2-fold (95% confidence interval: 2.5–7.0) higher likelihood of complex aortic lesions, with the likelihood little modified when controlling for cardiovascular risk factors. In particular, complex aortic lesions were found in 78% of patients with the highest carotid IMT tertile, compared with 14% of those with the lowest tertile (p<0.05). Based on these findings, carotid atherosclerosis is associated with aortic atherosclerosis, representing a risk factor for aortic lesions that are a potential ICVD risk. (Circ J 2003; 67: 597–600)

Key Words: Aorta; Atherosclerosis; Carotid arteries; Ultrasound

The recent clinical advent of transesophageal echocardiography (TEE) has allowed identification of occult embolic sources in the cerebral arteries, greatly contributing to the diagnosis of ischemic cerebrovascular disease (ICVD). Although TEE is primarily performed for the identification of the source of cardiac embolism, aortic lesions found thereby have been associated with the risk for ICVD. In particular, advanced arch lesions, such as mobile plaques, ulcers, and an intima-media thickness (IMT) greater than 4 mm, have been associated with the risk for cerebral embolism. On the basis of those studies, identification of aortic lesions may assist in clarifying the etiology of ICVD and, potentially, may prevent future events.

Carotid ultrasonography is a commonly used clinical tool for the diagnosis and risk assessment of ICVD because it enables noninvasive observation of atherosclerosis and an association between carotid and aortic atherosclerosis has been shown. In addition, TEE has shown that carotid artery stenosis often coexists in patients with aortic atheroma. However, advanced aortic lesions are frequently found in cases of ICVD without carotid stenosis. Accordingly, the factors predisposing to carotid and aortic atherosclerosis are not clearly separated, and whether carotid atherosclerosis is a marker for aortic lesions has not been determined. If noninvasive carotid imaging can identify complex aortic lesions, it may also provide additional information for the selection of candidates for TEE.

Carotid and aortic arch atherosclerosis is commonly evaluated by measuring the IMT on ultrasonography. The present study examined the association between carotid and aortic IMT in patients with ICVD, and investigated whether noninvasive carotid evaluation aids in the identification of complex aortic lesions that are a potential ICVD risk.

Methods

Subjects

The subjects for this investigation were enrolled from the ICVD patients admitted to Department of Internal Medicine and Therapeutics, Osaka University Hospital between July 1998 and August 2001. All patients had been referred from other clinics or departments for determination of the etiology of the ICVD and for its secondary prevention. During the study period, all ICVD patients underwent carotid ultrasonography and the majority of those also underwent TEE, except for those with the following criteria: (1) unequivocal etiology such as vertebral artery dissection and moyamoya disease, or (2) unlikely to benefit from TEE (eg, esophageal varices, terminal stages of malignancy). Additionally, because we wished to focus on the origin of the atherosclerosis, patients who had undergone carotid endarterectomy were excluded, as were those with Takayasu’s and other arteritis conditions. Accordingly, patients with posterior circulation infarct and those with a recognized
source of cardiac emboli were included in this study. After exclusion of 12 patients, based on our criteria, the study sample comprised 147 ICVD patients (age: 64±10 years), including 124 cases of ischemic stroke, 8 of transient ischemic attack and 15 of silent cerebral infarction.

This study conformed with the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all subjects after the nature of procedures had been fully explained.

**Carotid Ultrasoundography**

Duplex carotid ultrasoundography was performed with a linear array 7.5 MHz transducer (SSA-260A, Toshiba Inc, Tokyo, Japan). In accordance with other studies, the degree of carotid atherosclerosis was evaluated by measuring the maximum IMT of the common carotid artery or its bifurcation.

Briefly, the subject lay supine in a darkened room, and the examinations were done with the head held in the midline position or slightly tilted to the side. For the evaluation of IMT, the transducer was manipulated so that the near and far arterial walls were parallel to the transducer footprint and the lumen diameter was maximized in the longitudinal plane. The section with greatest IMT was visually identified on the far wall, where the maximum IMT was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. IMT was measured on the frozen frame of a suitable longitudinal image with the image magnified to achieve a higher resolution of detail. The contralateral carotid artery was examined following the same procedure, and the mean of both sides was used for analyses. Of note, the IMT measured in this study represents an indicator of earlier carotid atherosclerosis, and the increase in the IMT was found to identify complex aortic lesions.

**Transesophageal Echocardiography**

TEE was performed in accordance with standard protocols. After topical anesthesia of the oropharynx, a multiplane probe (SONOS 5500, Hewlett Packard Inc, Andover, OH, USA) was inserted into the esophagus, and the aortic wall was observed cross-sectionally and longitudinally. Subsequently, the aortic IMT (Ao-IMT) was measured at its maximum site in the proximal arch, as the distance between the lumen–intima interface and the media–adventitia interface. It was measured on the frozen frame, perpendicular to the vascular walls. The measurements were performed on both cross-sectional and longitudinal frames, and the mean value was used for analyses. In referring to the literature, an Ao-IMT ≥4 mm, mobile plaques and/or ulcers were defined as complex lesions with a potential ICVD risk. Mobile plaques were characterized by intraluminally protruding lesions with mobile components, and ulcers were diagnosed by the presence of large, obvious excavations (≥2 mm in depth and ≥2 mm in length) on the surface, with a well-defined back wall at its base.

All evaluations were performed by skilled stroke neurologists/cardiologists. Because TEE was performed as part of the routine clinical workup, the examiners were not completely unaware of the carotid findings. Thus, to reinforce the objectivity of the diagnoses, the aortic findings were always interpreted by 3 attendant examiners, with the final diagnoses made by consensus.

**Data Analyses**

Risk factors for the thickening of both the aortic and carotid IMT were explored by correlation analysis and unpaired t-test, followed by multiple linear regression analysis. The risk factors considered were age, sex, hypertension (casual blood pressure ≥160/95 mmHg or on medication), diabetes mellitus (fasting plasma glucose ≥7.77 mmol/L or on medication), hyperlipidemia (serum total cholesterol ≥5.70 mmol/L or on medication), and smoking. Smoking status was evaluated from self-reports, with a smoker defined by current or past smoking of more than 10 cigarettes/day for more than 1 year. Linear regression analysis was also used to examine the association between aortic and carotid IMT. Subsequently, the ability of carotid IMT to identify complex aortic lesions was examined by logistic regression analyses. Chi-square test was used to compare the frequency of complex aortic lesions across the tertiles of carotid IMT. Data are presented as mean±SD unless otherwise specified, and a two-tailed p value <0.05 considered statistically significant. All analyses were performed using SPSS 9.0 (SPSS Japan Inc, Tokyo, Japan).

**Results**

**Baseline Characteristics**

Because all patients had preceding ICVD, the prevalence of traditional cardiovascular risk factors was generally high in the study sample, with approximately 50% of patients having hypertension, hyperlipidemia or smoking habit (Table 1). As measures for aortic and carotid atherosclerosis, the average aortic and carotid IMT was 3.7±1.9 mm and 1.7±0.8 mm, respectively. In univariate analyses, values represent correlation coefficients for continuous variables, and mean±SD for dichotomic variables. In multivariate analyses, values represent standardized regression coefficients. *p<0.05.

**Table 1 Patients Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (years)</th>
<th>Sex (% men)</th>
<th>Hypertension (%)</th>
<th>Hyperlipidemia (%)</th>
<th>Diabetes mellitus (%)</th>
<th>Smoking habit (%)</th>
<th>Aortic IMT (mm)</th>
<th>Carotid IMT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>147</td>
<td>64±10</td>
<td>69</td>
<td>67</td>
<td>48</td>
<td>20</td>
<td>46</td>
<td>3.7±1.9</td>
<td>1.7±0.8</td>
</tr>
</tbody>
</table>

**Table 2 Risk Factors for the Thickening of Aortic and Carotid Intima–Media Thickness (IMT)**

<table>
<thead>
<tr>
<th></th>
<th>Aortic IMT</th>
<th>Carotid IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.46*</td>
<td>0.29*</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>4.1±1.9/3.0±1.6*</td>
<td>1.8±0.8/1.4±0.8*</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>3.9±1.8/3.4±2.0</td>
<td>1.8±0.9/1.4±0.7*</td>
</tr>
<tr>
<td>Hyperlipidemia (yes/no)</td>
<td>4.0±2.0/3.5±1.7</td>
<td>1.8±0.9/1.5±0.7*</td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td>3.9±1.6/3.7±2.0</td>
<td>1.8±0.7/1.7±0.8</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>4.3±1.8/3.3±1.9*</td>
<td>1.9±0.9/1.5±0.7*</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.47*</td>
<td>0.27*</td>
</tr>
<tr>
<td>Sex (men=1)</td>
<td>0.11</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.04</td>
<td>0.23*</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.16*</td>
<td>0.19*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.26*</td>
<td>0.23*</td>
</tr>
<tr>
<td>(Model R²)</td>
<td>(0.34)</td>
<td>(0.25)</td>
</tr>
</tbody>
</table>

IMT, intima–media thickness.
Risk Factors for the Thickening of Aortic and Carotid IMT

Both aortic and carotid IMT were moderately correlated with age, and greater in men than in women (Table 2). Also, they were generally greater in patients with cardiovascular risk factors than in those without. By multiple regression analysis, age, hyperlipidemia and smoking habit were found to be independently associated with both aortic and carotid IMT. Additionally, hypertension had an independent association with carotid IMT, but not with aortic IMT.

Associations Between Aortic and Carotid IMT

A moderate linear association was found between aortic and carotid IMT (Table 3, Fig 1). Although quadratic and cubic terms were also examined, the explicable variance was similar to that obtained by the linear term. After adjusting for age and sex, carotid IMT remained significantly associated with aortic IMT. When all cardiovascular risk factors were considered for the model, carotid IMT, age and smoking habit were found to be independently associated with aortic IMT.

Identification of Complex Aortic Lesions by Carotid IMT

Given the association between aortic and carotid IMT, noninvasive carotid evaluation may be able to identify aortic lesions that are a potential ICVD risk. To examine this, we performed logistic regression analyses, with the existence of complex aortic lesions as an endpoint. Because the relative risk appeared to increase log-linearly with carotid IMT (data not shown), we computed the odds ratio associated with 1 SD increase in carotid IMT. By univariate analysis, each SD greater carotid IMT was associated with 4.2-fold higher likelihood for complex aortic lesions (Table 4). Furthermore, the likelihood was only slightly attenuated when adjusting for age and sex, and additional cardiovascular risk factors. In the model including all such risk factors, carotid IMT and age were found to be significant predictors for complex aortic lesions. Additionally, there was a stepwise increase in the frequency of complex aortic lesions across the carotid IMT tertiles (Fig 2). In particular, complex aortic lesions were found in 38 of 49 (78%) patients in the highest tertile, compared with 7 of 49 (14%) patients in the lowest (p<0.05).

Discussion

We have shown an association between aortic and carotid atherosclerosis in ICVD, demonstrating the value of carotid evaluation for the identification of aortic lesions that are a potential ICVD risk.

Although both aortic and carotid atherosclerosis has been linked to a variety of cardiovascular risk factors, the factors predisposing to the pathology of the 2 arterial beds have not been clearly separated. In the current study, both aortic and carotid IMT increased with age, were greater in men, and appeared to have associations with traditional cardiovascular risk factors (Table 2), which has been shown elsewhere? Although hypertension had an independent association with carotid IMT, its association with aortic IMT was not significant when controlling for other risk factors. Based on this finding, hypertension has a stronger atherogenic effects on the carotid arteries than on the aortic arch;
however, our statistical power was limited, requiring much larger studies with refined criteria to establish this finding.

Despite the frequent coexistence of carotid stenosis in patients with aortic atherosclerosis,5,16 whether carotid findings can be used to stratify the severity of aortic atherosclerosis has not been established for ICVD. In the current study, we found a moderate linear relationship between aortic and carotid IMT (Fig 1), suggesting a link between aortic and carotid atherosclerosis. Moreover, the association was independent of age, sex and traditional cardiovascular risk factors (Table 3), further suggesting a linkage. In addition to carotid IMT, older age and smoking habit were independently associated with greater aortic IMT, supporting the study by Tribouilloy et al.10 Based on this result, older smokers with carotid atherosclerosis are more likely to have aortic arch atherosclerosis.

Kalikazaros et al have shown that carotid atheroma is predictive of aortic atheroma in cardiac patients. However, whether carotid lesions are predictive of aortic lesions that are a potential risk has not been fully established. Based on studies to date, complex aortic lesions, such as mobile plaques, ulcers and increased aortic IMT, are a greater risk for cerebral embolism3,5. In the current study, each 1 SD increase in carotid IMT was associated with 4.2-fold higher likelihood for complex aortic lesions (Table 4). Moreover, the likelihood was only slightly affected by age, sex and other cardiovascular risk factors. These findings suggest the value of carotid evaluation for the identification of the potential risk of aortic lesions. Because age was another predictor for such lesions independent of carotid IMT, such a prediction would be more robust in older individuals with greater carotid IMT. Additionally, it would be of clinical value to stratify the prevalence of complex aortic lesions by the carotid findings. The frequency of complex lesions increased in a stepwise fashion across the carotid IMT tertiles (Fig 2). Of note, complex aortic lesions were found in 78% of patients in the highest tertile, compared with 14% of those in the lowest. Based on this finding, the existence of an aortic source of emboli also needs to be considered when ICVD patients have increased carotid IMT. If such patients had embolic episodes of unknown origin, TEE would be the most effective modality for the exploration of ICVD etiology, with an additional caution for the observation of the aortic arch. Nonetheless, a considerable portion of the patients with less advanced carotid atherosclerosis had complex aortic lesions. Taken together, the severity of carotid atherosclerosis cannot be used as a definitive diagnostic marker for complex aortic lesions, but it can be a risk indicator for such lesions, potentially extending the benefit of routine carotid examination.

In patients with carotid atherosclerosis, silent cerebral infarction is often found not only in the ipsilateral, but also in the contralateral hemisphere.11,12 Given the association between aortic and carotid atherosclerosis, involvement of aortic lesions may need to be considered in the etiology of such infarction. Moreover, aortogenic cerebral embolism, whether symptomatic or asymptomatic, can occur during coronary or cerebral arteriography, and other aortic manipulations13–15 Based on our findings, carotid evaluation prior to the procedures may help in the assessment of procedure-related risk for cerebral embolism, when TEE is not available.

**Study Limitations**

First, all patients in this study had been referred for clarification of ICVD etiology, implying a potential bias in patient selection. For example, patients with only deep, small infarctions were less likely to be referred, precluding a generalization of the findings to all ICVD patients. Nonetheless, TEE is most often considered for patients with indeterminate ICVD etiology, which supports the clinical value of our findings. Second, we defined complex aortic lesions from existing evidence,13–15 but the strength of their association with ICVD etiology is not established, requiring further studies to validate that definition.

**Conclusion**

In patients with ICVD, carotid atherosclerosis is associated with aortic atherosclerosis, which represents a risk factor for aortic lesions that are a potential ICVD risk. Noninvasive carotid evaluation prior to TEE may aid in determining the existence of such aortic lesions.

**Acknowledgments**

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**References**