Combined Measurement of Carotid Stiffness and Intima-Media Thickness Improves Prediction of Complex Aortic Plaques in Patients With Ischemic Stroke

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Background and Purpose—We hypothesized that for the prediction or exclusion of aortic thrombi or plaques ≥4 mm, the combination of intima-media thickness (IMT) and distensibility (DC) of the common carotid arteries would be superior to the measurement of IMT alone.

Methods—We prospectively included 208 stroke patients (mean age, 60 years) undergoing transesophageal echocardiography for screening of aortic plaques. IMT and DC were determined by ultrasound, and DC was quantified by measuring blood pressure and the common carotid arteries diameter change on M-mode ultrasound during the cardiac cycle.

Results—Negative predictive values of IMT <0.9 mm and DC ≥24×10⁻²/kPa for the exclusion of aortic atheroma ≥4 mm were similar (92.0% and 91.7%, respectively). However, negative predictive values increased to 98.2% and to 100.0% for the exclusion of aortic thrombi when both parameters were combined. Positive predictive values of IMT ≥0.9 mm and DC <24 were lower (46.3%, 41.1%; respectively), but they also increased in combination (54.3%).

Conclusions—Our findings suggest that IMT and DC represent different vessel wall properties and that measuring both parameters provides optimized characterization of carotid atherosclerosis. Combining IMT and DC increases the predictive power of carotid ultrasound, making transesophageal echocardiography dispensable for assessment of the aorta for those with normal carotid arteries and indispensable for those patients with carotid atherosclerosis. (Stroke. 2006;37:2708-2712.)

Key Words: aortic plaques ■ carotid arteries ■ distensibility ■ intima-media thickness ■ transesophageal echocardiography

Carotid intima-media thickness (IMT) and distensibility (DC) represent structural and functional vessel wall properties, but the pathophysiological mechanism of their correlation is unclear: a strong linkage of the 2 markers as well as the possibility of 2 independent processes have been discussed.¹

Increased IMT and decreased DC are correlated with generalized atherosclerosis,¹,² and both of them are strong predictors of ischemic stroke.³⁻⁵ In the Rotterdam study, carotid stiffness and IMT were furthermore related to aortic plaque thickness.¹ However, in that population-based study with a high mean age, aortic plaques were judged by abdominal x-ray, thus detecting only advanced stages of atherosclerosis. To date, only a few studies have addressed the link between carotid and aortic atherosclerosis by ultrasound techniques in detail and have investigated the predictive values derived from the easily accessible carotid arteries. In a previous study, we demonstrated that a normal carotid IMT excluded aortic high-risk sources of cerebral embolism, such as thrombi or plaques ≥4 mm, thus making transesophageal echocardiography (TEE) dispensable for assessment of the aorta.⁶ However, in concordance with others,⁷ positive predictive values were low.

The aim of this study was thus (1) to evaluate the predictive power of carotid DC for complex aortic plaques, ie, aortic thrombi or plaques ≥4 mm, and (2) to investigate whether the combination of DC and IMT would increase the predictive values compared with IMT measurement alone.

Subjects and Methods

Study Population and Cardiovascular Risk Factors

Patients (N=208) with acute cerebral ischemia admitted to our stroke unit fulfilled the 3 inclusion criteria, ie, age 18 to 85 years, presence of acute brain ischemia, and performance of TEE, and were prospectively included. The indication for TEE was derived from recommendations of a previous study.⁸ TEE was scheduled when...
routine diagnostic tests (eg, transthoracic echocardiography, ECG, extracranial/intracranial ultrasound) could not clarify the stroke etiology. On an individual basis, patients with equivocal etiology after routine diagnostic tests (eg, moderate internal carotid artery stenosis) also underwent TEE.

The local ethics committee approved the study, and all patients gave written, informed consent. Cardiovascular risk factors were prospectively documented and defined as described previously.7 Infarct etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria in each patient after completion of the diagnostic work-up.5

**Duplex Sonography of Carotid Arteries**

**Intima-Media Thickness**

Carotid arteries were assessed by duplex ultrasound with a 7- to 12-MHz linear-array scanner (ATL, HDI 5000) by 1 trained sonographer. The subject was examined in the supine position. When an optimal longitudinal image of the common carotid artery (CCA) was obtained, it was frozen in magnification on the R-wave of the ECG and stored on S-VHS videotape. The IMT was measured 4 times on the optimal longitudinal image of the common carotid artery (CCA) was defined as the overall mean IMT of 16 sides of the CCA at a plaque-free site. For each individual, the IMT was measured 4 times on the R-wave of the ECG. Dd indicates maximal diastolic diameter, and Ds, maximal systolic diameter.

**Distensibility Coefficient**

CCA stiffness (ie, DC) was determined in M-mode by assessing the maximal change in diameter during systole and diastole as

$$DC = \frac{2 \times \Delta d}{Dd \times \Delta P} \times 10^{-3} [kPa],$$

where \(\Delta d\) is the change in diameter, \(Dd\) the end-diastolic diameter, and \(\Delta P\) the pulse pressure (Figure 1). Measurement was performed 2 cm proximal to the carotid bifurcation at a plaque-free site. Arterial blood pressure was obtained noninvasively and simultaneously with a Dinamap blood pressure-measuring device. Pulse pressure (\(\Delta P\)) was calculated as the difference between maximal systolic and diastolic blood pressures derived from the average of 4 measurements. A DC of 24\(\times10^{-3}\)kPa was chosen as the cutoff between normal and decreased DC because it represented the average value of all included patients. Patients were further subcategorized into 4 groups: 1, normal IMT and DC; 2, normal IMT but decreased DC; 3, increased IMT but normal DC; and 4, increased IMT and decreased DC.

Quantitative measurements of IMT and DC were performed offline. The readers of ultrasound images from the videotape were blinded to patient demographics and the results of TEE examinations.

**Transthoracic and Transesophageal Echocardiography**

The protocol for echocardiography has been described previously.8 In brief, the ultrasound system (ATL, HDI 3500) and a 5-MHz transducer were used for the TEE examinations. The ascending aorta and the aortic arch, including the outlet of the left subclavian artery, were examined by TEE with respect to aortic plaques defined as an irregular, intimal thickening with increased echogenicity. The thickest plaque was considered for classification. Aortic thrombus was defined as a laminated deposit along the intimal surface, with variable echogenicity, and which might be associated with mobile lesions. According to the results of a previous study,3 patients with an aortic wall thickness (AWT) \(\geq 4\) mm were in group 1, those with an AWT > 1 to 3.9 mm were in group 2, and those with an AWT \(\geq 4\) mm were in group 3. Aortic thrombi superimposed on plaques or aortic atheroma \(\geq 4\) mm thick were defined as complex plaques. Echocardiograms were stored on videotape, and the cardiologist was blinded to the duplex sonography findings and the patients’ demographic data.

**Statistical Analysis**

Data are presented as the mean and SD for continuous variables and as absolute and relative frequencies for categorical variables. To detect statistically significant relations between categorical variables, Fisher’s exact test was used. For continuous variables, t tests or Wilcoxon tests were applied as appropriate. For comparison of 2 groups, a 1-way ANOVA was used. Correlations of selected vari-

### TABLE 1. Baseline Characteristics of the Study Population and the 4 Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients, n=208</th>
<th>Group 1, n=57</th>
<th>Group 2, n=43</th>
<th>Group 3, n=27</th>
<th>Group 4, n=81</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 (±13.3)</td>
<td>66.5 (±13.6)</td>
<td>62.1 (±8.2)</td>
<td>68.7 (±6.9)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>95 (45.7)</td>
<td>30 (52.6)</td>
<td>20 (46.5)</td>
<td>6 (22.2)</td>
<td>39 (48.1)</td>
<td>0.058</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>138 (66.3)</td>
<td>20 (35.1)</td>
<td>29 (67.4)</td>
<td>19 (70.4)</td>
<td>71 (87.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>44 (21.2)</td>
<td>1 (1.8)</td>
<td>11 (25.6)</td>
<td>8 (29.6)</td>
<td>24 (29.6)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hyperlipidemia, No. (%)</td>
<td>77 (37.0)</td>
<td>10 (17.5)</td>
<td>20 (46.5)</td>
<td>11 (40.7)</td>
<td>37 (45.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>58 (27.9)</td>
<td>25 (43.9)</td>
<td>11 (25.6)</td>
<td>9 (33.3)</td>
<td>13 (16.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Coronary heart disease, No. (%)</td>
<td>39 (18.8)</td>
<td>5 (8.8)</td>
<td>8 (18.6)</td>
<td>8 (29.6)</td>
<td>18 (22.2)</td>
<td>0.073</td>
</tr>
<tr>
<td>Peripheral artery disease, No (%)</td>
<td>12 (5.8)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
<td>2 (7.4)</td>
<td>9 (11.1)</td>
<td>0.018</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack, No. (%)</td>
<td>23 (11.1)</td>
<td>1 (1.8)</td>
<td>6 (14.0)</td>
<td>2 (7.4)</td>
<td>14 (17.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>137 (±21.3)</td>
<td>121 (±15.7)</td>
<td>140 (±17.6)</td>
<td>127 (±11.8)</td>
<td>149 (±20.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73 (±9.7)</td>
<td>70 (±8.4)</td>
<td>76 (±10.6)</td>
<td>71 (±6.9)</td>
<td>74 (±10.3)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Subgroups are defined in text. \(\pm\)Values are SD.
Correlation of Carotid and Aortic Atherosclerosis

Atherosclerosis Cardioembolism

Large-Artery Small-Vessel Other Determined Undetermined 
Atherosclerosis Disease Etiology Etiology Etiology 
P
n (%) 15 (7.2) 72 (34.6) 22 (10.6) 13 (6.3) 86 (41.3) <0.0001

IMT, mm

1.04 (±0.22) 1.00 (±0.20) 0.97 (±0.21) 0.73 (±0.14) 0.81 (±0.17) <0.0001

AWT, mm

3.55 (±1.91) 4.42 (±1.80) 2.48 (±1.06) 1.87 (±1.13) 2.08 (±1.16) <0.0001

DC, 10^-3/kPa

19.93 (±6.84) 20.24 (±9.24) 22.34 (±8.02) 27.59 (±10.47) 26.57 (±11.27) 0.0006

AWT ≥4 mm, No. (%) 4 (26.7) 48 (66.7) 3 (13.6) 0 (0.0) 4 (4.7) <0.0001

Values are SD.
undergo TEE examination to screen for a probable source of cerebral emboli.

IMT is widely used as a surrogate end point for determining the success of interventions that lower risk factors for atherosclerosis.\textsuperscript{12,13} In contrast, only a few small studies\textsuperscript{14–16} have investigated the effect of statin therapy on carotid DC, and no clinical trials to date have investigated the influence of optimal therapy of cardiovascular risk factors on both carotid IMT and compliance. Our results suggest that measuring both parameters would improve the characterization of atherosclerosis in both the carotid arteries and the aorta and serve as a more sensitive marker of progression and regression of atherosclerosis in clinical trials than IMT measurement alone. Furthermore, measuring both parameters could also help select those patients requiring earlier and more aggressive antiatherogenic treatment.

The exact linkage of IMT and DC in the development of atherosclerosis is unknown so far, but several hypothesis have been discussed: (1) The presence of atherosclerosis leads to stiffening of arteries; (2) Increased arterial stiffness causes wall damage and atherosclerosis owing to the loss of shock-absorbing capacity; (3) Both mechanisms apply, leading to a self-perpetuating and reinforcing process; or (4) Atherosclerosis and arterial stiffness are 2 independent processes.\textsuperscript{1} The better correlation of AWT with the combination of IMT and DC and the equal predictive values of both parameters suggest 2 independent processes. However, only IMT was an independent predictor of AWT in our study. Future longitudinal studies evaluating the development of IMT increase and the DC decrease over time might clarify this point.

The predictive value of IMT found in this study is slightly lower than in our previous study,\textsuperscript{6} which might have been attributable to the fact that we performed TEE only in those patients without clarified stroke etiology after routine diagnostic testing; ie, patients with $\geq80\%$ stenosis of the internal carotid artery or atrial fibrillation were not included. Therefore, a certain number of patients with progressive atherosclerosis of the carotid arteries and the aorta are not represented.

**Limitations of the Study**

We did not include stroke patients consecutively, which might have caused a bias in patient selection. Also, we arbitrarily chose the mean value of DC in our cohort as the cutoff for predictive values, because normal values for a larger cohort were unavailable. Therefore, the predictive

### TABLE 4. Multivariate Regression Analysis of Carotid and Aortic Ultrasound Measurements From Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DC, n=208</th>
<th>AWT, n=208</th>
<th>AWT $\geq$4, mm n=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC</td>
<td>...</td>
<td>0.371</td>
<td>0.249</td>
</tr>
<tr>
<td>IMT</td>
<td>0.014</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>$&lt;0.001$</td>
<td>0.257</td>
<td>0.219</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.932</td>
<td>0.647</td>
<td>0.838</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.244</td>
<td>0.766</td>
<td>0.356</td>
</tr>
<tr>
<td>Age $\geq$60 y</td>
<td>$&lt;0.001$</td>
<td>0.053</td>
<td>0.519</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.594</td>
<td>0.219</td>
<td>0.347</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.523</td>
<td>0.036</td>
<td>0.112</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.032</td>
<td>0.112</td>
<td>0.341</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.102</td>
<td>$&lt;0.001$</td>
<td>0.003</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.056</td>
<td>0.387</td>
<td>0.203</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>0.327</td>
<td>0.773</td>
<td>0.801</td>
</tr>
<tr>
<td>History of stroke/transient ischemic attack</td>
<td>0.018</td>
<td>0.018</td>
<td>0.148</td>
</tr>
</tbody>
</table>

$P$ values for the test of no effect of the corresponding characteristics on the dependent variables are shown.
values of DCs might change with different cutoff values and different study populations. Normal values should be evaluated by high-resolution ultrasound techniques analogous to the determination of IMT in previous studies.17

Conclusions
Carotid IMT and DC seem to represent different atherosclerotic vessel wall properties. Measuring both parameters provides optimal characterization of atherosclerosis and could thus provide a more sensitive surrogate marker of carotid atherosclerosis for future trials investigating the influence of treatment on the progression of atherosclerosis. Also, the combination of IMT and DC of the CCAs increases the predictive power of ultrasound, making TEE dispensable for assessment of the aorta in normal carotid arteries but indispensable in patients with carotid atherosclerosis.

References
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