Impact of Aortic Stiffness on Ischemic Stroke in Elderly Patients

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Background and Purpose—Large atherosclerotic plaques in the aortic arch detected by transesophageal echocardiography (TEE) are associated with increased risk of ischemic stroke in the elderly. The atherosclerotic process also affects aortic distensibility, which can also be assessed by TEE. The purpose of this study was to evaluate the possible association of aortic stiffness by TEE with ischemic stroke in elderly patients.

Methods—We performed TEE in 40 consecutive elderly patients aged ≥55 years with acute ischemic stroke and in 42 consecutive control subjects aged ≥55 years. Aortic stiffness index β, which has been used in the literature to express the stiffness of the aortic wall, was calculated as follows: β = ln (systolic blood pressure/diastolic blood pressure)/((D_max − D_min)/D_min), where ln is natural logarithm, D_max is maximum aortic lumen diameter, and D_min is minimum aortic lumen diameter by TEE. The association of index β with ischemic stroke was evaluated by logistic regression analysis after adjustment for potential confounders, including thickness of aortic arch plaques.

Results—Index β was significantly greater in stroke patients than in controls (9.7 ± 5.0 versus 5.3 ± 3.5; P < 0.0001). When aortic plaque thickness and other stroke risk factors were entered in multivariate analysis, index β was found to be independently associated with ischemic stroke (odds ratio, 1.28 per unit increase; 95% CI, 1.10 to 1.52).

Conclusions—Aortic stiffness by TEE is associated with ischemic stroke, independent of thickness of aortic arch plaques and other stroke risk factors. This suggests that aortic stiffness by TEE may add prognostic information when assessing the risk of ischemic stroke in the elderly. (Stroke. 2002;33:2077-2081.)

Key Words: aorta ■ cerebrovascular disorders ■ echocardiography, transesophageal ■ stroke, ischemic

Ischemic stroke is the second most common cause of death worldwide.1 It is also the third leading cause of mortality in the United States and Europe and a leading cause of serious, long-term disability.2,3 The presence of atherosclerotic plaques in the aortic arch detected by transesophageal echocardiography (TEE) predicts the risk of ischemic stroke in the elderly.4–6 The atherosclerotic process also affects aortic elastic properties, which can also be assessed by TEE.7–10 Assessment of aortic stiffness by TEE may therefore provide useful information for assessing the risk of ischemic stroke. However, few data are available regarding the impact of aortic stiffness on the risk of ischemic stroke. Thus, in the present study we evaluated the effect of the aortic stiffness of thoracic aorta by TEE on ischemic stroke risk in elderly patients.

Subjects and Methods

The patient population of this study consisted of 40 patients aged ≥55 years with acute ischemic stroke, consecutively referred for TEE. Control subjects (n = 42) were consecutive stroke-free volunteers aged ≥55 years. Patients with previous stroke or transient ischemic attack, aortic dissection, or other aortic disease were excluded. Cases and controls were drawn from the National Institute of Neurological Disorders and Stroke–sponsored Aortic Plaque and Risk of Ischemic Stroke (APRIS) study. This study was approved by the Institutional Review Board of Columbia-Presbyterian Medical Center, and written informed consent was obtained from all patients.

Diagnostic Evaluation

Stroke risk factors were collected by direct interview or medical record review in all stroke patients and control subjects. Arterial hypertension was defined as the presence of a positive history or antihypertensive treatment or blood pressure value > 140/90 mm Hg. Hypercholesterolemia was defined as a total serum cholesterol > 240 mg/dL or the presence of appropriate drug treatment. Diabetes mellitus was defined on the basis of positive history or the presence of oral or insulin treatment. Coronary artery disease definition included history of myocardial infarction or typical angina, the presence of a positive diagnostic test (stress test, coronary angiography), or drug treatment.

The cardiac evaluation included 12-lead ECG and 2-dimensional color Doppler transthoracic echocardiography. The neurological workup in patients with stroke included head CT or MRI, carotid and vertebral artery duplex Doppler ultrasonography, and transcranial Doppler examination of the middle and anterior cerebral arteries or basilar artery. Cerebral angiography was performed when clinically indicated.
Detection of Aortic Plaques

TEE was performed in a systematic fashion as previously described. The test was performed with the use of Hewlett-Packard Sonos 5500 ultrasound equipment with biplane or multiplane transducer at 5 MHz (Hewlett-Packard Imaging Systems Division). The aortic arch was defined as the portion of aorta between the curve at the end of the ascending aorta and the origin of the left subclavian artery. Plaques were defined as a discrete protrusion of the intimal surface of the vessel 2 mm in thickness and different in appearance and echogenicity from the adjacent intact intimal surface. The presence and location of any plaques were recorded on VHS videotape. In the cases of multiple plaques, the most advanced lesion was considered. The videotapes were reviewed by a single experienced echocardiographer who was blinded to case-control status. An example of plaque measurement is provided in Figure 1.

Measurement of Aortic Stiffness

To assess aortic stiffness index $\beta$, we recorded on VHS videotape aortic images at the level of proximal descending thoracic aorta using TEE-guided M mode, and we measured blood pressure by cuff sphygmomanometry simultaneously. Maximum aortic lumen diameter during ejection period ($D_{max}$) and minimum aortic lumen diameter during preejection period ($D_{min}$) were measured (Figure 2).

The aortic arch was defined as the portion of aorta between the curve at the end of the ascending aorta and the origin of the left subclavian artery. Plaques were defined as a discrete protrusion of the intimal surface of the vessel ≥2 mm in thickness and different in appearance and echogenicity from the adjacent intact intimal surface. The presence and location of any plaques were recorded on VHS videotape. In the cases of multiple plaques, the most advanced lesion was considered. The videotapes were reviewed by a single experienced echocardiographer who was blinded to case-control status. An example of plaque measurement is provided in Figure 1.

Statistical Analysis

Aortic stiffness index $\beta$ was compared between stroke patients and control subjects. Differences between mean values were assessed by unpaired Student’s $t$ test. Since $\beta$ index was not normally distributed in the study population, the Mann-Whitney test was used in the independent analyses regarding index $\beta$. A 2-tailed value of $P<0.05$ was considered significant. The association of $\beta$ with ischemic stroke was evaluated by multivariate logistic regression analysis after...
adjustment for stroke risk factors and other pertinent variables (age, sex, hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, coronary artery disease). Adjusted odds ratios and 95% CI were calculated from the \( β \) coefficients and the standard errors. All analyses were performed with the use of SAS statistical package version 6.12.

**Results**

**Patient Characteristics**
The characteristics of stroke patients and control subjects are presented in Table 1. Stroke patients were significantly older than control subjects \((P<0.05)\). Sex distribution was similar between the 2 groups. The analysis of stroke risk factors revealed a significantly greater prevalence of hypertension and diabetes mellitus in stroke patients than in control subjects.

**Aortic Stiffness, Thickness of Aortic Arch Plaques, and Ischemic Stroke**
Aortic stiffness index \( β \) was significantly greater in stroke patients than in controls \((9.7±5.0 \text{ mm Hg versus } 5.3±3.5 \text{ mm Hg}; P<0.0001)\) (Figure 3A). Thickness of aortic arch plaques was also significantly greater in stroke patients than in control subjects \((3.6±2.5 \text{ mm versus } 2.2±2.1 \text{ mm}; P<0.01)\) (Table 2). A significant increase in stroke risk was observed with increased thickness of aortic plaques \((\text{adjusted odds ratio, 1.43 per millimeter increase in thickness; 95% CI, 1.04 to 1.95})\). In all subjects, \( β \) weakly correlated with age \((r=0.40, P<0.001)\) (Figure 3B), systolic blood pressure \((r=0.40, P<0.001)\) (Figure 3C), and thickness of aortic plaques \((r=0.38, P<0.001)\) (Figure 3D). When other potential confounders and thickness of aortic plaques were included in a multivariate analysis, \( β \) was found to be independently associated with ischemic stroke \((\text{adjusted odds ratio, 1.28 per unit increase; 95% CI, 1.10 to 1.52})\).

**Discussion**
In this study we showed that aortic stiffness determined by TEE is associated with ischemic stroke in elderly patients after adjustment for the presence of other established stroke risk factors. This suggests that the assessment of aortic stiffness by TEE may be useful for predicting ischemic stroke risk.

**Aortic Stiffness and Atherosclerosis**
In 1904, Marchand recognized the consistent association of fatty degeneration and vessel stiffness and introduced the term *atherosclerosis* to indicate that they are closely linked. 18 Blankenhorn and Kransch then suggested that further

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**Table 1. Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Stroke Patients</th>
<th>Control Subjects</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69±9</td>
<td>65±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male sex</td>
<td>18 (45%)</td>
<td>20 (48%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (78%)</td>
<td>19 (45%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (50%)</td>
<td>9 (21%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>16 (40%)</td>
<td>24 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>5 (13%)</td>
<td>6 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12 (30%)</td>
<td>7 (17%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are number (%), except for age.

**Table 2. Blood Pressure, Aortic Lumen Diameter, Aortic Stiffness, and Aortic Arch Plaque Thickness**

<table>
<thead>
<tr>
<th></th>
<th>Stroke Patients</th>
<th>Control Subjects</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>155±24</td>
<td>143±21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83±11</td>
<td>79±15</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic Dmax, mm</td>
<td>24.8±2.5</td>
<td>25.0±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic Dmin, mm</td>
<td>23.8±2.6</td>
<td>23.1±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic stiffness index ( \beta )</td>
<td>9.7±5.0</td>
<td>5.3±3.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque thickness, mm</td>
<td>3.6±2.5</td>
<td>2.2±2.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean±SD.

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**Figure 3.** A, Comparison of aortic stiffness between controls and stroke patients. Aortic stiffness index \( β \) was significantly increased in patients with ischemic stroke compared with control subjects. B, Correlation between aortic stiffness index \( β \) and age. C, Correlation between aortic stiffness index \( β \) and systolic blood pressure. D, Correlation between aortic stiffness index \( β \) and plaque thickness in the aortic arch.
studies of atherosclerosis should use a combination of measures to evaluate both atherosclerosis and sclerosis, therefore including functional changes in arterial stiffness. Currently, most diagnostic techniques to detect atherosclerosis focus on the atheromatous component, which is represented by morphological changes of the arterial wall. An example is the assessment of plaque deposition or thickening arterial wall in the aorta and carotid arteries.20-23 The sclerotic component, or the physical information provided by the assessment of arterial stiffness, is not as often evaluated. Although these 2 components are interconnected, studies examining the association between arterial physiological changes and morphological changes have yielded conflicting results, confirming7-20,23 or denying24,25 a close association. Therefore, it is important that both components be evaluated when looking for possible early predictors of atherosclerosis.7,9

TEE Assessment of Aortic Stiffness
The search for cardioembolic sources of ischemic stroke is currently one of the most common indications for TEE. TEE allows simultaneous and quantitative assessment of morphological and physiological properties of the thoracic aorta. This method is accurate in the measurement of aortic stiffness because it provides high-quality images of the thoracic aorta. The existence of a simple exponential relation between the logarithm of relative pressure and the distension ratio in the arteries has been observed, and the slope of this relation has been shown to represent a vascular stiffness index by in vitro studies.15,16 The index β is considered to be independent of the operating blood pressure and the entire deformation behavior of the vascular wall, and a proper parameter to express the vascular stiffness over the physiological wide range of systemic blood pressure. This index has been used in TEE studies that have estimated the aortic vascular stiffness in humans.7-10,20

Aortic Stiffness, Plaques, and Risk of Ischemic Stroke
Recently, several studies have reported that patients with cardiovascular disease have increased aortic stiffness compared with patients without it.26-28 Furthermore, it has been shown that aortic stiffness is an independent predictor of all-cause and cardiovascular mortality.29,30 However, few data are available regarding the impact of aortic stiffness on ischemic stroke. In our study we showed that aortic stiffness is independently associated with ischemic stroke. A recent study suggested that there is a proportional progression of arterial stiffness at different sites of the arterial tree.39 An increased aortic stiffness might reflect physiological vascular dysfunction in the cerebral circulation, which might help to explain the association between aortic stiffness and stroke we observed.

Several studies have demonstrated that the thickness and complexity of aortic arch plaques are strongly associated with ischemic stroke in the elderly, probably through increased frequency of cerebral embolization.4-6,12-14 In the present study frequency and thickness of aortic plaques were greater in patients with stroke than in control subjects. Stiffness index β was weakly but significantly correlated with aortic plaque thickness. However, index β remained independently associated with stroke after adjustment for established stroke risk factors, including aortic arch plaque thickness. Although the presence of large aortic arch plaques detected by TEE is a powerful predictor of stroke risk, the prevalence of large aortic plaques in elderly subjects with stroke only ranges between 14% and 45% in various studies.4-6,13,14 On the other hand, aortic stiffness can be evaluated in all patients who undergo TEE, adds only a few minutes to the duration of the test, and may provide information on stroke risk even in patients without evidence of aortic arch plaques. Aortic stiffness may therefore be a useful adjunctive tool in assessing the risk of ischemic stroke, providing an early measure of increased risk when significant plaques are not yet identifiable.

As a limitation to our study, it should be noted that our study group was relatively small, and our data may therefore need to be confirmed in larger patient populations.

Conclusions
We demonstrated that aortic stiffness, as determined by TEE, is associated with ischemic stroke in the elderly, independent of the presence of aortic arch plaques and other stroke risk factors. This suggests that the assessment of aortic stiffness may provide useful information in predicting stroke risk in elderly patients undergoing TEE, whether or not an aortic plaque is also found.

Acknowledgments
This study was supported in part by grants from the National Institute of Neurological Disorders and Stroke (R01 NS36286, NS29993, T32NS07153).

References


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Stroke. 2002;33:2077-2081
doi: 10.1161/01.STR.0000021410.83049.32

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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