CLINICAL STUDIES

Protruding Atherosclerotic Aortic Plaques and Dyslipidaemia: Correlation to Subtypes of Ischaemic Stroke

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Aims: To evaluate whether thoracic aortic plaques together with dyslipidaemia are related to ischaemic stroke, and if so, to which of the subtypes of stroke.

Methods and Results: We performed transoesophageal echocardiography in 50 patients with acute ischaemic stroke and in 401 controls. The aorta was divided into two segments: (1) the proximal, proximal to the left subclavian artery, and (2) the distal aorta. Protruding plaques (Intima-media thickness ≥4 mm in thickness) in the proximal aorta were detected in 14 of the 50 patients (28%) with stroke, and in 53 of the 401 controls (13%) (P<0.01). Plaque score in the proximal aorta (2.1 ± 1.8 vs 0.9 ± 0.7; P<0.05), low-density lipoprotein cholesterol level (3.60 ± 0.85 vs 2.87 ± 0.72 mmol/l; P<0.05), and apolipoprotein B/A-I ratio (0.98 ± 0.17 vs 0.73 ± 0.16; P<0.005) were higher in patients with atherothrombotic than in cardioembolic stroke. The score in the proximal aorta correlated with low-density lipoprotein cholesterol level (r=0.44, P<0.005) and apolipoprotein B/A-I ratio (r=0.40, P<0.01).

Conclusion: Severe plaques in the proximal aorta together with dyslipidaemia are seen more frequently in patients with atherothrombotic stroke. Lipid analysis may contribute to the prediction and the treatment of the patients who are at high risk for atherothrombotic stroke.

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Key Words: Aortic plaque; dyslipidaemia; ischaemic stroke; transoesophageal echocardiography.

Introduction

Transoesophageal echocardiography is a useful tool for evaluating thoracic aortic atherosclerosis[1–12]. Atherosclerotic plaques in the ascending aorta and the aortic arch detected by transoesophageal echocardiography have been regarded as important predictors of ischaemic stroke[2,4,7,10,11]. Although these atherosclerotic plaques have been reported to be sources of cerebral emboli, particularly when they are ≥4 mm in thickness[2,4], the relation of atherosclerotic plaques to different subtypes of ischaemic stroke remains undetermined.

The development of atherosclerosis is strongly associated with dyslipidaemia. Dyslipidaemia is related to aortic atherosclerosis detected by transoesophageal echocardiography[11,12]. In addition, cholesterol lowering therapy is shown to regress aortic atherosclerosis in patients with familial hypercholesterolaemia[5,6]. The role of dyslipidaemia in the development of ischaemic stroke remains somewhat unclear[13–15], though therapy with statin drugs has been reported to reduce risk of...
ischaemic stroke\textsuperscript{15}. The relation of dyslipidaemia to different subtypes of ischaemic stroke also remains to be determined\textsuperscript{13,15}.

The purpose of this study was to evaluate whether atherosclerotic aortic plaques together with dyslipidaemia are related to ischaemic stroke, and if so, to which of the subtypes of ischaemic stroke.

**Methods**

**Study Population**

We studied 50 patients [34 men and 16 women, (mean age 65 ± 11 years)] with acute ischaemic stroke who were hospitalized between 1996 and 1998. The diagnosis of ischaemic stroke was made by findings on neurological examination and demonstration of ischaemic lesions on computed tomography, according to the criteria of Cerebrovascular Disease III by the National Institute of Neurological Disorder and Stroke\textsuperscript{16}. Patients with aortic disease, such as aortic dissection or aortic aneurysm, were excluded. Severe liver disease, renal disease, abnormal thyroid function, as well as patients taking steroids were not considered for this study.

The control group consisted of 401 patients [229 men and 172 women, (mean age 63 ± 10 years)] with no history of ischaemic stroke who were referred to our laboratories for transoesophageal echocardiography to assess cardiac conditions. The patients with acute ischaemic stroke and controls did not differ with respect to mean age, and left ventricular systolic function.

The presences of the following factors were also recorded: hypercholesterolaemia, hypertension, diabetes mellitus, history of smoking, and atrial fibrillation. Hypercholesterolaemia was defined as a fasting total cholesterol level >5.69 mmol/l. Hypertension was defined as either systolic pressure ≥160 mmHg or diastolic pressure ≥90 mmHg. Diabetes was defined as hyperglycaemia requiring ongoing pharmacological therapy. History of and current cigarette smoking were considered significant.

**Transoesophageal echocardiography Examination and Analysis**

Two-dimensional transoesophageal echocardiography was performed using TOSHIBA SSH160A and ALOKA SSD-870 ultrasound equipments with commercially available 5 MHz multiplane (n=190), biplane (n=211) or monoplane (n=50) transducers. After examining cardiac structures, the thoracic aorta was carefully examined. All studies were recorded on super VHS videotape for subsequent review and analysis. All 451 studies on the recorded tapes were analysed and graded by two independent cardiologists with extensive experience in transoesophageal echocardiography who had no knowledge of clinical results. Any discrepancy was resolved by consensus.

We defined the proximal aorta as that including the ascending aorta and aortic arch, and the distal aorta as the descending aorta. The maximal intimal thickness was measured separately in the ascending aorta, the aortic arch, and the descending aorta. Intima ≥4 mm in thickness was defined as protruding plaque.

In patients with ischaemic stroke, atherosclerosis in each of these three segments was graded on a scale of 0 to 2, respectively; i.e., normal intima was defined as score 0, thickened intima ≤4 mm in thickness as score 1, and thickened intima ≥4 mm in thickness as score 2. In addition, one more score was added when the thickened intima had either irregular surface or mobile component. We calculated the atherosclerotic aortic plaque score in the proximal aorta (as the sum of the score in the ascending aorta and the aortic arch), and the score in the distal aorta.

**Subtypes of Ischaemic Stroke**

Subtypes of ischaemic stroke were based on the classification previously described\textsuperscript{16}, i.e., cardioembolic as large cortical infarction with a cardiac source of emboli but without severe cerebrovascular atherosclerosis, atherothrombotic as cortical infarction without a cardiac source of emboli, lacunar stroke as a subcortical small infarction <15 mm in diameter, or unclassified. The following cardiac sources of embolism were defined: (1) atrial fibrillation, (2) spontaneous echo contrast, (3) recent myocardial infarction, (4) intracardiac thrombi, (5) left ventricular dysfunction, (6) prosthetic heart valves, and (7) mitral or aortic valve disease. Lacunar is a common type of ischaemic stroke in Japan seen more frequently than in western countries\textsuperscript{17}.

**Apolipoprotein Analysis**

Blood samples for the assessment of apolipoprotein profile were obtained in the morning after an overnight fast within two days of admission in the 50 patients with acute ischaemic stroke. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride were measured by enzymatic methods using an automatic analyser (Hitachi). Low-density lipoprotein cholesterol was calculated using Friedwald’s formula\textsuperscript{18}. The concentration of serum apolipoprotein A-I and B were also measured by turbidmetric immunoassay using an automatic analyser (Daiichi Chaemicals). Apolipoprotein B/A-I ratio was calculated.

**Statistical Analysis**

Results were expressed as mean ± SD. A chi-square test was used to compare categorical variables. Group data were compared using the unpaired Student’s t-test or analysis of variance (ANOVA) with Fisher’s PLSD test where appropriate. Linear regression analysis was used.
to compare continuous variables. A P value <0.05 was considered statistically significant.

### Results

#### Subtypes of Ischaemic Stroke

Cardioembolic was found in 12 patients, atherothrombotic in 14, lacunar in 20, and unclassified stroke in four.

#### Clinical Characteristics of Patients with Ischaemic Stroke and Controls

The clinical characteristics of patients and controls are shown in Table 1. There were no significant differences in clinical characteristics between the two groups.

#### Aortic Plaques in Patients with Ischaemic Stroke and Controls

The echocardiographic findings in patients and controls are shown in Table 2. Protruding plaques in the proximal aorta were detected in 14 of the 50 patients (28%) with ischaemic stroke, and in 53 of the 401 controls (13%) (P<0.01). Protruding plaques in the distal aorta were detected in 16 of the 50 patients (32%) with ischaemic stroke, and in 41 of the 401 controls (10%) (P<0.001). The incidence of protruding plaques was higher in patients with ischaemic stroke than in controls, both in the proximal and the distal aorta. There were no significant differences in the incidences of thrombus and spontaneous echo contrast in the left atrium between the two groups.

#### Aortic Plaques and Apolipoprotein Profile in Association with Subtypes of Ischaemic Stroke

Atherosclerotic scores in the proximal and the distal aorta among the three subtypes of ischaemic stroke.

The atherosclerotic scores in the proximal and the distal aorta among the three subtypes of ischaemic stroke are shown in Table 2. Protruding plaques in the proximal aorta were detected in 14 of the 50 patients (28%) with ischaemic stroke, and in 53 of the 401 controls (13%) (P<0.01). Protruding plaques in the distal aorta were detected in 16 of the 50 patients (32%) with ischaemic stroke, and in 41 of the 401 controls (10%) (P<0.001). The incidence of protruding plaques was higher in patients with ischaemic stroke than in controls, both in the proximal and the distal aorta. There were no significant differences in the incidences of thrombus and spontaneous echo contrast in the left atrium between the two groups.

#### Lipid profiles

Lipid profiles are shown in Table 3. Low-density lipoprotein-cholesterol level (3.60 ± 0.85 vs 2.87 ± 0.72 mmol/l, P<0.05) was significantly higher in patients than in controls. Apolipoprotein B/A-I ratio was also higher in patients than in controls (0.73 ± 0.16 vs 0.91 ± 0.24).

### Table 1. Clinical characteristics of patients with ischaemic stroke and controls.

<table>
<thead>
<tr>
<th></th>
<th>Stroke (n=50)</th>
<th>Controls (n=401)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 11</td>
<td>63 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>34 (68%)</td>
<td>229 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>8 (16%)</td>
<td>82 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (34%)</td>
<td>126 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (28%)</td>
<td>68 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (30%)</td>
<td>125 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13 (26%)</td>
<td>124 (31%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2. Echocardiographic findings in patients with ischaemic stroke and controls.

<table>
<thead>
<tr>
<th></th>
<th>Stroke (n=50)</th>
<th>Controls (n=401)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous echo contrast</td>
<td>9 (18%)</td>
<td>60 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombus</td>
<td>1 (2%)</td>
<td>8 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal plaques</td>
<td>14 (28%)</td>
<td>53 (13%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Distal plaques</td>
<td>16 (32%)</td>
<td>41 (10%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 3. Lipid profile in association with subtypes of ischaemic stroke.

<table>
<thead>
<tr>
<th></th>
<th>Cardioembolic (n=12)</th>
<th>Atherothrombotic (n=14)</th>
<th>Lacunar (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.48 ± 0.80</td>
<td>5.18 ± 0.88</td>
<td>5.05 ± 1.06</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.11 ± 0.28</td>
<td>0.93 ± 0.13</td>
<td>0.93 ± 0.20</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.06 ± 0.38</td>
<td>1.38 ± 0.59</td>
<td>1.26 ± 0.51</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.87 ± 0.72</td>
<td>3.60 ± 0.85*</td>
<td>3.52 ± 0.95</td>
</tr>
<tr>
<td>Apolipoprotein B/A-I</td>
<td>0.73 ± 0.16</td>
<td>0.98 ± 0.17**</td>
<td>0.91 ± 0.24</td>
</tr>
</tbody>
</table>

HDL=high-density lipoprotein, LDL=low-density lipoprotein.
*P<0.05, **P<0.005 vs cardioembolic.
Lipoprotein-cholesterol. Low-density lipoprotein-
Total plasma cholesterol comprises the sum of lipopro-
been reported to add important information to the risk
Therefore, lipoprotein and apolipoprotein analyses have
stroke[2,4,7,10,11]. The relative risk correlated with the
of mobile plaque components[5]. Superimposed throm-
embolism. Thus, therapy should be aimed at preventing
plaque rupture, decreasing the embolic potential of the
and promoting healing of the mobile component. Lowering the cholesterol concentration
macrophage activity and accumulation of chol-
esterol, and improves endothelial dysfunction, making
aortic plaque more stable and less likely to fissure[22].
Recent studies have demonstrated that cholesterol low-
tering therapy leads to regression of atherosclerosis in
coronary arteries[21], carotid arteries[23], and the thoracic aorta[3,6], although it was modest at best. It has also been shown that statins e-
effectively reduce the risk of ischaemic stroke[15], as well as coronary events[24], probably by restoring their endothelial function through exerting anti-thrombotic effects[25], and/or by stabilizing atherosclerotic plaques. Lowering the cholesterol concentration may be a useful treatment for the patients who are at high risk for atherothrombotic stroke.

Limitations

Firstly, the echocardiograms in this study were done with monoplane, biplane, and multiplane transducers. Although monoplane and biplane transducers could be inferior to the currently available multiplane transducers in visualizing complex anatomy, transoesophageal echocardiography, even with a multiplane transducers, may miss a small area of the aorta that is masked by the air column in the trachea and this may have reduced the number of aortic plaques found. A multiplane transducer was used in all patients with ischaemic stroke, but used in 140 controls. It is possible that the use of a multiplane transducer would have increased the yield somewhat. However, the aortic score was calculated only in patients with ischaemic stroke. Also, care was
taken to obtain good images of the aorta and detect aortic plaques using monoplane and biplane transducers with proper angulation. Secondly, our atherosclerotic score may not always reflect the severity and extent of atherosclerosis, since there is still no standard grading system. Thirdly, lipid data in patients with ischaemic stroke may be affected by the timing of testing. In this study, lipid analysis was performed within 2 days of admission of patients with ischaemic stroke. A recent report has suggested that lipid profiles should ideally be assessed within the first 2 days of the onset of ischaemic stroke to avoid inaccurate measurement.[26] Finally, a small number of patients with ischaemic stroke were studied. Our results thus need to be confirmed in a larger study population.

Conclusions
Severe plaques in the proximal aorta together with dyslipidaemia are seen more frequently in patients with atherothrombotic stroke. Although aortic plaques may simply be markers for generalized atherosclerosis, including concomitant cerebrovascular atherosclerosis, protruding plaques in the proximal aorta could be possible embolic sources in atherothrombotic stroke. Lipid analysis may contribute to the prediction and the treatment of the patients who are at high risk for atherothrombotic stroke.

Acknowledgement
This study was presented in part at the 70th Annual Scientific Session of the American Heart Association, Orlando, November, 1997.

References
[22] Brown BG, Zhao XQ. Importance of endothelial function in mediating the benefits of lipid-lowering therapy. Am J Cardiol 1998; 82: 49T–52T.