Predictive Value of Inflammatory and Hemostatic Parameters, Atherosclerotic Risk Factors, and Chest X-Ray for Aortic Arch Atheromatosis

Philipp Ehlermann, MD; Wladimir Mirau, MD; Jürgen Jahn, MD; Andrew Remppis, MD; Abdolhamid Sheikhzadeh, MD

Background and Purpose—Aortic arch atheromatosis (AAA) is a common cause of cerebral embolism. Transesophageal echocardiography (TEE) shows not only the extension of atherosclerotic plaques but also the mobility of superimposed thrombi. In most cases AAA is only detected after the embolic event. This study was therefore designed to identify predictive factors for AAA.

Methods—One hundred seven consecutive patients referred for routine TEE were included in the study. Patients on warfarin therapy, with a history of recent surgery, or with any signs of infectious, immunological, or malignant diseases were excluded.

Results—Diabetes mellitus carried the highest risk for AAA (odds ratio, 3.0), followed by hyperlipidemia (2.5) and arterial hypertension (2.3). Age >70 years was accompanied with a 1.8-fold increased risk. Patients with aortic calcifications on standard chest x-ray had a 4.6-fold higher prevalence. Severe AAA was associated with higher levels of C-reactive protein (14.6±14.1 versus 4.9±7.2 mg/L), fibrinogen (4.20±1.22 versus 3.45±1.29 mg/L), plasmin/antiplasmin complexes (728±297 versus 453±243 μg/L), and D-dimers (980±632 versus 444±349 μg/L).

Conclusions—AAA is accompanied by elevation of inflammatory and hemostatic parameters. Patients with classic cardiovascular risk factors and aortic calcifications on chest x-ray have a higher prevalence. Further prospective studies are now warranted to establish a risk score to identify patients in whom TEE screening should be undertaken. (Stroke. 2004;35:34-39.)

Key Words: aorta ▪ atherosclerosis ▪ echocardiography ▪ risk factors

At the beginning of the last decade, it was recognized that aortic arch atheromatosis (AAA) is an important cause of cerebral and peripheral embolism.1 Consequently, AAA was shown to be significantly associated with stroke and peripheral embolism,2-4 while the prevalence of atherosclerotic lesions in patients with previous embolic events was 27%.5 Moreover, it was found that the incidence of neurological events correlates with the severity of atherosclerosis and echocardiographic criteria such as plaque thickness, lesion mobility, and superimposed thrombi.6 In a prospective echocardiographic study, an incidence of vascular events of 13.7% in patients with complex aortic plaques was found.7 AAA is thus an important cause of cerebral embolisms, accounting for nearly 30% of hitherto unexplained or “cryptogenic” strokes.

Transesophageal echocardiography (TEE) is the current reference method for plaque imaging, providing real-time images showing the mobility of superimposed thrombi.8 Although some complementary imaging techniques exist, TEE is the sensitive and cost-effective method of choice for diagnosis of AAA.9 The indication for TEE and other imaging techniques such as MRI for recognition of AAA, however, is mainly established only after an embolic event has already occurred or if other cardiac diseases are present. Because the number and the average age of patients undergoing cardiac catheterization and coronary bypass surgery are increasing and these interventions always carry the risk of cerebral embolizations due to manipulations at the aortic arch, it would be desirable to identify patients at risk.10,11 Since similar pathophysiological mechanisms underlie both coronary artery disease (CAD) and AAA, we hypothesized that classic CAD risk factors might also predict AAA. It was therefore the aim of this study to evaluate clinical, radiological, inflammatory, and procoagulation parameters involved in atherosclerosis.
that may predict AAA before embolic events or other complications occur.

Subjects and Methods

Patients
To exclude the influence of other concomitant diseases that might influence inflammatory and coagulation parameters, all patients with acute thromboembolic events or surgery 8 weeks before TEE study, established or suspected infectious endocarditis, prosthesis valves, malignancy, any infectious or immunological disease, atrial thrombi, acute coronary symptoms, or any liver disease were excluded, as were those on oral anticoagulant therapy (eg, warfarin). Aspirin intake or heparin administration was not an exclusion criterion. Finally, 107 patients (71 men [66%] and 36 women [34%]) gave informed consent and were included prospectively into the study. Indications for TEE were history of possible embolism (n = 71), prior electric cardioversion (n = 16), exclusion of aortic dissection (n = 6), evaluation of valves (n = 5), abdominal aneurysm (n = 4), suspected ventricular septum defect (n = 2), and others (n = 8).

Risk Factors
Diabetes mellitus (fasting glucose $\geq$ 120 mg/dL or under treatment), arterial hypertension (repeated diastolic pressures $\geq$ 90 mm Hg, repeated diastolic pressures $\geq$ 90 mm Hg, or under treatment), hyperlipidemia (total fasting cholesterol $>6.5$ mmol/L or under treatment), smoking (>10 packages per year), and obesity (body mass index $>28$ kg/m²) were assessed as risk factors for AAA. All patients were evaluated for previously established concomitant cardiovascular diseases such as CAD, peripheral vascular disease, carotid stenosis, transient ischemic attack, and stroke. CAD was defined as history of myocardial infarction, revascularization therapy, or confirmed stenosis of $>50\%$ of vessel lumen. Peripheral vascular disease was defined by any imaging or Doppler technique confirming a significant stenosis. Carotid stenosis was defined by lumen narrowing of $>50\%$.

Chest Roentgenograms
Standard chest roentgenograms of sufficient quality, in which the interval between TEE and x-ray did not exceed 4 weeks, were available from 84 patients. These images were screened for aortic calcifications according to Kulke and classified into band-type and plaque-type calcifications.

Transesophageal Echocardiography
The full sequence of all TEE studies was documented on a videotape. Aortic plaques were classified according to plaque thickness and structure as intimal thickening $<2$ mm (grade I), thickening $>2$ mm and $<5$ mm (grade II), thickening $>5$ mm (grade IIIa), and plaque with mobile components regardless of plaque thickness (grade IIIb). Plaque morphology in terms of echogenicity, defined as reflectance of the emitted ultrasound signal, was graded into predominantly echolucent, predominantly echogenic, intermediate, or calcified plaques. The vessel lumen was used as reference for defining echolucency, and the bright echo zone produced by the media-adventitia interface was used as reference for echogenicity. As for the chest x-rays, TEE studies were evaluated by the same 2 investigators (W.M. and A.S.), who were blinded regarding the patient’s history. In case of discrepancies, classification was performed after consent.

For assessment of interobserver and intraobserver variability, 39 randomly selected TEE tapes of 107 studies were reviewed twice in a randomized order by 2 investigators (P.E. and A.R.), who were blinded to each other and to the previous results. The results were compared for agreement regarding plaque grading and morphology.

Laboratory Parameters
Blood was collected in the morning from patients in a supine position, in a fasting and resting state. Plastic tubes with 3.8% trisodium-citrate and lithium-heparin (Sarstedt) were used. After immediate centrifugation at 2000g for 15 minutes, plasma was frozen at $-80^\circ$C until use. Plasma C-reactive protein (CRP) was determined on a Dade Behring nephelometer with the use of the N-latex high-sensitivity CRP kit. Hemostatic markers were assayed with the use of commercially available enzyme-linked immunosorbent assay kits (Dade Behring), except antithrombin III (Coastest, Chromogenix), fibrinogen (Electra 1000 C, Baxter), von Willebrand factor antigen (Roche), and dimerized plasmin fragment D (D-dimer) (Roche). All global coagulation tests were assayed on a BCS automatic coagulation analyzer (Dade Behring). All measurements were performed in duplicate.

Statistical Analysis
The SPSS software package (version 9.0 for Windows) was used for statistical analyses. Differences in mean values between groups by plaque grading and morphology were compared by ANOVA. Significance of trends was tested by linear regression or by $\chi^2$ test for trend. Two-sided probability values of $P<0.05$ were considered significant.

Results

Clinical Characteristics
A total of 107 patients were included into the study. The mean age was 67 years (range, 50 to 88 years). Most patients (n = 71) underwent TEE to find a source of embolism or for exclusion of left atrial thrombi before cardioversion. The classic risk factor diabetes mellitus was present in 27 patients (25.2%), arterial hypertension in 62 (57.9%), hyperlipidemia in 41 (38.3%), smoking in 29 (27.1%), and obesity in 15 (14.0%). Concomitant coronary heart disease was present in 61 patients (57.0%), carotid stenosis in 13 (12.1%), and peripheral vascular disease in 16 (15.0%).

Transesophageal Echocardiography
Twenty-six patients (24.3%) had no atherosclerotic changes of the thoracic aorta. Fifty-nine patients (55.1%) had severe atherosclerotic changes (grade IIIa and IIIb), whereas 30 (28.0%) had lesions showing mobile structures (grade IIIb) due to plaque rupture or superimposed thrombi. Echolucent plaques were found in 41 patients, predominantly at grades IIIa and IIIb of AAA (Table 1). Patients with higher grades of AAA were significantly older than those with other grades. The same observation was made for echolucent plaques.

For assessment of interobserver and intraobserver variability, 39 randomly selected TEE tapes of 107 studies were reviewed twice in a randomized order by 2 investigators (P.E. and A.R.), who were blinded to each other and to the previous results. The results were compared for agreement regarding plaque grading and morphology.

TABLE 1. AAA Gradings and Different Plaque Morphologies

<table>
<thead>
<tr>
<th>Grade</th>
<th>I</th>
<th>II</th>
<th>IIIa</th>
<th>IIIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echolucent</td>
<td>0</td>
<td>4</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hyperechogen</td>
<td>1</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Calcified</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Twenty-six patients had no atherosclerotic changes (grade 0).

The risk for AAA was significantly increased for diabetes mellitus (2.96-fold), hyperlipidemia (2.54-fold), and arterial hypertension (2.33-fold). Patients with established CAD had a 2.52-fold higher prevalence for AAA (Figure 1). No significance was seen for smoking and obesity, but the 30 nicotine-using patients were significantly younger (63 ± 8 years) than the 82 patients who abstained from nicotine (69 ± 9 years).
The same tendency was seen in the 16 obese patients (62±7 versus 68±9 years).

Full agreement between the initial assessment and the 2 reviewers was found in 67% for grading and in 72% for morphology. Intraobserver agreement was obtained in 94% for grading and 87% for morphology. Most discrepancies were due to assessment of mobility and if plaque extension was close to the limits of 2 and 5 mm.

Chest Roentgenograms
Sufficient chest roentgenograms were available in 84 of 107 patients. Forty-one of these patients had signs of aortic calcifications. Thirteen patients, who displayed both band-type and plaque-type calcifications, showed higher grades of AAA (II, 3; IIIa, 8; IIIb, 2). In 22 patients with only band-type calcifications, 4 patients had no AAA and 2 had less severe grades of AAA. Five patients had exclusively plaque-type calcifications, all of which were graded IIIa and IIIb on TEE. Among patients without any signs of calcification on x-ray, 7 had AAA grade IIIa and 9 patients had grade IIIb (Figure 2). Thus, for x-ray, sensitivity of 66%, specificity of 70%, positive predictive value of 74%, and negative predictive value 62% were calculated. The relative risk for AAA in patients showing any calcification of the aortic shape was 4.58 compared with patients showing no calcifications (Figure 1). Plaque-type calcifications were slightly more likely to be associated with AAA than band-type calcifications.

Hemostatic and Inflammatory Parameters
Highest levels of CRP were found in patients with extended aortic plaques, including mobile parts (Figure 3). A similar observation was made for fibrinogen, plasmin-antiplasmin complexes, and D-dimers. Antithrombin III levels were lower in patients with higher grades of AAA. Within other hemostatic parameters, no differences between several AAA grades were found for prothrombin time, activated partial thromboplastin time, protein C, protein S, and thrombin-antithrombin complexes. Prothrombin fragments 1 and 2 tended to be higher in patients with grade IIIb (Table 2).

Since higher grades of AAA were correlated with more echolucent plaque morphology, it was not surprising that for echolucent plaques the same changes of coagulation parameters were seen as for higher grades of AAA. However, a marked difference was observed for von Willebrand factor antigen, which was significantly increased in patients with echolucent plaques compared with controls (Table 3). In patients with echodense plaques, this difference failed to reach significance (P=0.057).
carotid stenosis. Our results show that clinical presentation of the thrombogenic aorta includes advanced age, risk factors for atherosclerotic diseases, and concomitant vascular diseases such as CAD. In our study population, the number of patients with peripheral vascular disease or carotid stenosis was too small to gain significance. As in our study, advanced age, diabetes, arterial hypertension, and hyperlipidemia are reported as independent predictors of thrombogenic aorta. Patients with nicotine abuse and obesity were significantly younger in our study. This may have resulted in a false, nonsignificant risk reduction in obese and smoking patients.

Typical calcifications of the aortic knob on routine chest x-ray are often associated with AAA. However, these radiological criteria alone do not provide sufficient sensitivity or specificity to predict aortic atheromatosis. Only patients with heavily calcified aortic knobs are reported to have AAA in 91% of cases. False-positive results of chest x-ray may be due to extravascular calcifications, while a negative x-ray may miss uncalcified echolucent plaques, which are particularly prone to embolic complications. The absence of calcification in hypoechoic aortic plaques was found to be associated with a markedly increased risk of embolism, as was also seen for echolucent stenotic plaques of the carotids. This may be explained by the observation that these plaques are lipid laden and therefore more vulnerable.

Changes in coagulation or inflammatory parameters may be helpful if any other pathophysiological mechanism can be ruled out. These parameters include procoagulation or fibrinolytic factors such as D-dimers, prothrombin fragments 1 and 2, plasmin/antiplasmin complexes, and inflammatory markers such as CRP and fibrinogen. Our study shows that atheromatosis of the aorta is associated with activation of coagulation and fibrinolysis. Parameters such as D-dimers, activated factor II, prothrombin fragments 1 and 2, and plasmin/antiplasmin complexes were elevated at higher grades of AAA. Prothrombin fragments

### Table 2. Laboratory Findings in Patients With Different Grades of Aortic Atheromatosis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Age, y</th>
<th>CRP, mg/L</th>
<th>PT-INR</th>
<th>PTT, sec</th>
<th>FIBR, g/L</th>
<th>vWF-Ag, %</th>
<th>ATIII, %</th>
<th>ProtC, %</th>
<th>F1U2, nmol/L</th>
<th>TAT, µg/L</th>
<th>DDIM, µg/L</th>
<th>PAP, µg/L</th>
<th>ProTS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62.4±9.3</td>
<td>4.9±7.2</td>
<td>1.21±0.38</td>
<td>3.45±1.29</td>
<td>94±24</td>
<td>120±32</td>
<td>8.5±1.52</td>
<td>113±41</td>
<td>1.03±0.80</td>
<td>11.5±15.3</td>
<td>644±349</td>
<td>453±243</td>
<td>93±19</td>
</tr>
<tr>
<td>1</td>
<td>65.4±6.0</td>
<td>6.2±4.5</td>
<td>1.27±0.20</td>
<td>3.73±1.48</td>
<td>118±14</td>
<td>110±36</td>
<td>0.70±0.58</td>
<td>113±41</td>
<td>1.32±23.3</td>
<td>8.9±15.4</td>
<td>321±74</td>
<td>354±182</td>
<td>119±3</td>
</tr>
<tr>
<td>2</td>
<td>65.3±10.3</td>
<td>6.0±3.8</td>
<td>1.11±0.20</td>
<td>4.18±1.36</td>
<td>92±21</td>
<td>139±29</td>
<td>0.90±0.43</td>
<td>113±41</td>
<td>13.2±23.3</td>
<td>8.9±15.4</td>
<td>390±225</td>
<td>383±162</td>
<td>108±21</td>
</tr>
<tr>
<td>3</td>
<td>70.2±6.7</td>
<td>10.7±10.8</td>
<td>1.0±0.16</td>
<td>3.99±1.28</td>
<td>106±11</td>
<td>139±33</td>
<td>1.03±0.80</td>
<td>113±41</td>
<td>11.5±15.3</td>
<td>8.9±15.4</td>
<td>517±342</td>
<td>453±181</td>
<td>107±17</td>
</tr>
</tbody>
</table>

CRP indicates C-reactive protein; PT-INR, prothrombin time-international normalized ratio; PTT, partial thromboplastin time; FIBR, fibrinogen; vWF, von Willebrand factor antigen; ATIII, antithrombin III; ProtC, protein C; F1U2, prothrombin fragments 1 and 2; TAT, thrombin-antithrombin III complexes; DDIM, D-dimers; PAP, plasmin/antiplasmin complexes; ProTS, protein S.

*P<0.001 vs grade 0; †P<0.01 vs grade 0; ‡P<0.05 vs grade 0.

### Table 3. Laboratory Findings in Patients With Different Plaque Morphologies

<table>
<thead>
<tr>
<th>No Plaque</th>
<th>Calculated</th>
<th>Echodense</th>
<th>Intermediate</th>
<th>Echolucent</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 26</td>
<td>n = 5</td>
<td>n = 22</td>
<td>n = 14</td>
<td>n = 40</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.4±9.3</td>
<td>65.4±8.7</td>
<td>68.5±8.8</td>
<td>68.3±8.2</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>4.9±7.2</td>
<td>8.0±1.56</td>
<td>8.6±10.1</td>
<td>9.5±11.5</td>
</tr>
<tr>
<td>FIBR, g/L</td>
<td>3.45±1.29</td>
<td>3.60±0.49</td>
<td>4.20±1.58</td>
<td>3.91±0.94</td>
</tr>
<tr>
<td>vWF-Ag, %</td>
<td>120±32</td>
<td>111±24</td>
<td>134±28</td>
<td>122±35</td>
</tr>
<tr>
<td>DDIM, µg/L</td>
<td>444±349</td>
<td>225±50</td>
<td>363±274§</td>
<td>458±351</td>
</tr>
<tr>
<td>PAP, µg/L</td>
<td>453±243</td>
<td>383±145</td>
<td>406±187†</td>
<td>517±274</td>
</tr>
</tbody>
</table>

*P<0.001 vs no plaque; †P<0.01 vs no plaque; ‡P<0.05 vs no plaque; §P<0.001 vs echolucent; ||P<0.01 vs echolucent.

Abbreviations as in Table 2.
1 and 2 suggest an increased generation of thrombin by cleavage from prothrombin. The fibrinolytic activity at higher grades of AAA was increased, as indicated by elevated levels of D-dimers. Differences were also seen for fibrinogen levels since this parameter was shown to be an independent risk factor in another study.\textsuperscript{27} The same trend for laboratory markers as for increasing grades was seen for different plaque morphologies. Echolucent plaques tended toward higher proinflammatory and procoagulation parameters, but echolucent plaques were predominantly found at higher grades. Interestingly, elevated levels of von Willebrand factor antigen were observed, particularly in patients with echolucent plaques. Von Willebrand factor is involved in thrombus formation, particularly in conditions of high shear stress,\textsuperscript{28} which is typically found within the aortic arch. Since atherosclerosis is a systemic disease, atherosclerotic manifestations in other vascular regions are expected to show similar effects on laboratory parameters. The high prevalence of this finding warrants careful consideration not only of existing AAA in patients undergoing procedures such as cardiac catheterization or bypass surgery, since these are associated with the risk of central embolism, but also of the importance of AAA as a clinical finding, shown by the fact that the majority of patients with cryptogenic embolism presented with AAA. Thus, although the results of the present study seem predictable because most of the patients had suspected embolism, the aim of the study was to elucidate the clinical view of AAA and to prepare for future studies focusing on noninvasive risk scoring.

A major limitation of this study is that recruitment of patients was dependent on other reasons for TEE. Because it was necessary to exclude all diseases that influence inflammatory and procoagulation parameters, the patients included in the study are a selected group. Furthermore, the prevalence of concomitant cardiovascular diseases may have been underestimated because it was derived from the patients’ histories. In particular, classification of plaque morphology is subject to interobserver variability and is dependent on the complexity of the classification used. Reproducibility may vary between 50\% and 90\% in different studies.\textsuperscript{29,30} Therefore, we selected 39 of 107 studies for assessment of interobserver and intraobserver variability. We found a significant interobserver variability, while intraobserver variability was satisfactory. Therefore, an advantage of our study was that all TEE studies were reviewed by the same investigators. On the basis of the results of this study, a further prospective study in which screening for AAA in a general population is the only reason for TEE is now warranted.

In conclusion, in patients with atherosclerotic risk factors, advanced age, CAD, carotid atherosclerosis, typical changes of aorta on x-ray, and unexplained hypercoagulable or inflammatory state, physicians should be aware of atherosclerotic manifestations such as AAA. Further prospective studies are now warranted to establish a risk score to identify patients who may profit from a screening TEE.

Acknowledgment
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References


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