Aortic Spontaneous Echocardiographic Contrast and Hemostatic Markers in Patients With Nonrheumatic Atrial Fibrillation*

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Objectives: To determine the relationship between spontaneous echocardiographic contrast (SEC) in the descending thoracic aorta and plasma levels of hemostatic markers in patients with nonrheumatic atrial fibrillation (AF).

Design and settings: A cross-sectional study at a university hospital.

Patients and measurements: In 91 consecutive patients (mean ± SE age, 70 ± 1 years; 68 men) with nonrheumatic AF who underwent transesophageal echocardiography, plasma levels of markers for platelet activity (platelet factor 4 [PF4] and β-thromboglobulin [β-TG]), thrombotic status (thrombin-antithrombin III complex [TAT]), and fibrinolytic status (D-dimer and plasmin-α2-plasmin inhibitor complex [PIC]) were determined.

Results: Forty-three patients who had aortic SEC (AoSEC) were older (72 years vs 68 years; p < 0.05) and had a higher prevalence of chronic AF (88% vs 52%; p < 0.05) than 48 patients without AoSEC. TAT, PIC, and D-dimer levels were significantly higher in patients with AoSEC than in those without AoSEC, whereas PF4 and β-TG levels were not different between the two groups. Although the prevalence of cerebral embolism did not differ between the two groups (23% vs 29%), the prevalence of peripheral embolism was higher in patients with AoSEC than in those without AoSEC (10% vs 0%; p < 0.05). Multivariate analysis revealed mitral regurgitation (odds ratio, 7.53; p < 0.02), SEC in the left atrium (odds ratio, 2.14; p < 0.02), and aortic atherosclerosis (odds ratio, 1.87; p < 0.04) emerged as independent predictors of AoSEC.

Conclusions: Patients with nonrheumatic AF who have AoSEC appear to have enhanced coagulation activity but not platelet activity. Intensive anticoagulation treatment might be required for these patients.

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Key words: aorta; atrial fibrillation; embolism; hemostatic markers; spontaneous echocardiographic contrast; transesophageal echocardiography

Abbreviations: AF = atrial fibrillation; AoSEC = aortic spontaneous echocardiographic contrast; β-TG = β-thromboglobulin; LA = left atrium; LASEC = spontaneous echocardiographic contrast in the left atrium; PF4 = platelet factor 4; PIC = plasmin-α2-plasmin inhibitor complex; SEC = spontaneous echocardiographic contrast; TAT = thrombin-antithrombin III complex; TEE = transesophageal echocardiography

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spontaneous echocardiographic contrast (SEC) in the left atrium (LA) and LA appendage observed by transesophageal echocardiography (TEE) is a well-known predictor of thromboembolism in patients with nonrheumatic atrial fibrillation (AF) and reflects low flow and hypercoagulable states in the LA. SEC has been observed not only in the LA or other cardiac chambers but also in the aorta. Several studies have reported an association between aortic SEC (AoSEC) and risk of thromboembolism. A study by the Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography reported that complex aortic plaque emerged as a risk factor of thromboembolism in patients with nonrheumatic AF and that warfarin was effective in reducing stroke in patients with AF and complex aortic plaque.

Hemostatic markers might be effective in evaluating the hypercoagulable state in patients at risk of
thromboembolism. Patients with nonrheumatic AF show higher levels of hemostatic markers in sinus rhythm compared with control subjects. However, it remains unclear whether AoSEC is associated with the hypercoagulable state as determined by plasma levels of hemostatic markers. Therefore, in the present study, we determined a possible relationship between plasma levels of hemostatic markers and TEE findings of the thoracic aorta including AoSEC in patients with nonrheumatic AF.

### Materials and Methods

#### Study Patients

Of 138 consecutive patients (100 men and 38 women; mean ± SE age, 69 ± 1 years) with nonrheumatic AF who underwent TEE and determination of plasma levels of hemostatic markers, 91 patients (68 men; age, 70 ± 1 years) with AF at the time of TEE were selected. The indication for TEE was an evaluation of the potential thromboembolic risk or identification of the cardiogenic source of recent embolism. Underlying diseases included the following: hypertension (n = 17), ischemic heart disease (n = 10), hypertrophic cardiomyopathy (n = 4), dilated cardiomyopathy (n = 7), sick sinus syndrome (n = 11), Wolff-Parkinson-White syndrome (n = 4), mitral valve prolapse (n = 8), and miscellaneous diseases (n = 9). No apparent underlying diseases were identified in the 21 patients. Baseline clinical characteristics, including body mass index, diabetes mellitus, hyperlipidemia, and cigarette smoking, were determined from medical records and routine laboratory findings. The use of oral antplatelet or anticoagulant at the time of echocardiographic studies was carefully determined. All patients underwent brain CT or MRI to determine the presence of embolic cerebral infarction.

#### Echocardiography

All patients underwent transthoracic echocardiographic and TEE studies after giving informed consent. Transthoracic echocardiography was performed using a 3.75-MHz, phased-array transducer connected to an ultrasound system (SSH-140A; Toshiba; Tokyo, Japan). LA dimension, left ventricular end-diastolic and end-systolic dimensions, and left ventricular ejection fraction were determined by M-mode echocardiography according to the standards of the American Society of Echocardiography. The presence of moderate to severe mitral regurgitation was evaluated by color flow imaging of the jet with a 2.5-MHz, phased-array transducer. TEE was performed with a 5-MHz multplane transducer connected to the same ultrasound system. Each patient was studied in the fasting state without any premedication except for topical anesthesia of the hypopharynx with lidocaine spray. Multiple standard tomographic planes were imaged. Subsequently, LA appendage peak flow velocity, presence of LA thrombi, and severity of SEC in LA (LASEC) were determined. The presence of LA thrombi and the severity of SEC were determined by two independent observers. Any difference in the determination was resolved by the opinion of a third observer.

#### LASEC and LA Appendage Flow

LASEC was diagnosed in the presence of dynamic smoke-like echoes within LA or the LA appendage with a characteristic swirling motion that was distinct from the white noise artifact. The severity of LASEC was defined by the criteria of Fatkin et al.: 0 = none (absence of echogenicity); 1+ = mild (minimal echogenicity detectable only transiently during the cardiac cycle with optimal gain settings); 2+ = mild to moderate (transient spontaneous echocardiographic contrast without increased gain settings and more dense pattern than 1+); 3+ = moderate (dense swirling pattern during the entire cardiac cycle); and 4+ = severe (intense echodensity and very slow swirling patterns in the LA appendage, usually with a similar density in the main LA cavity). LA appendage flow-velocity profiles were obtained by pulsed-wave Doppler echocardiographic interrogation at the orifice of the appendage. Peak outflow velocity signals within each R-R interval were averaged over a minimum of six cardiac cycles.

#### AoSEC, Aortic Atherosclerosis, and Distensibility

AoSEC was diagnosed in the presence of dynamic smoke-like echoes within the descending thoracic aorta with a characteristic swirling motion as in the case of LASEC. The influences of the white noise artifact were also carefully excluded. Aortic atherosclerosis was evaluated using the grading system of Montgomery et al.: grade I = no disease or intimal thickening; grade II = intimal thickening; grade III = atheroma < 5 mm; grade IV = atheroma ≥ 5 mm; and grade V = any mobile atheroma. Aortic distensibility was evaluated by measuring systolic and diastolic aortic diameters, and relative change in the aortic diameter was calculated. The severity of atherosclerosis was determined by two independent observers.

#### Blood Sample Collection

The following hemostatic markers were determined: platelet factor 4 (PF4) and β-thromboglobulin (β-TG) levels as indexes of platelet activation, thrombin-antithrombin III complex (TAT) as a marker of thrombin activity, and D-dimer and plasmin-α₂-plasmin inhibitor complex (PIC) as indexes of active fibrinolysis. Blood sampling was carried out on the day of the TEE study using the two-syringe technique. The first 2 to 3 mL of blood were discarded, and the subsequent samples were collected in a sequential manner directly into syringes containing the appropriate anticoagulant mixture and then processed immediately. The anticoagulant mixtures for β-TG and PF4 contained theophylline, adenosine, dipyridamole, and sodium citrate. Mixtures of 2.7 mL of blood and anticoagulants were centrifuged at 3,000 rpm for 20 minutes, and supernatants were stored at −20°C until assayed. β-TG, PF4, and TAT levels were measured with enzyme immunoassay kits (Behring Werke AG; Marburg, Germany). The D-dimer level was measured with enzyme-linked immunosorbent assay kits (Behring Werke AG). The PIC level was measured using latex photometric immunoassay kits.

#### Brain CT and MRI

In all patients, brain CT or MRI was performed to determine the presence of embolic cerebral infarction. Cerebral infarction was diagnosed by a neurologist without any knowledge of the TEE findings. Cortical infarction was regarded as cerebral embolism, and infarction in the territories of deep perforators was excluded from the following analysis because this specific type of infarction was probably caused by cerebral thrombosis.
Statistical Analysis

Values are presented as means ± SE. Student’s unpaired t test was used to compare continuous variables between the two groups. The χ² test or Fisher’s Exact Probability Test, if indicated, was used to compare the categoric variables. Nonparametric variables were compared using the Mann-Whitney test. Multivariate logistic regression analysis was performed to identify independent risk factors of AoSEC using statistical software (SPSS 8.0-J; SPSS; Chicago, IL). Results of multivariate analysis are expressed as odds ratios for the comparison of risk between the 10th and 90th percentiles (with 95% confidence intervals). A p value < 0.05 was considered significant.

RESULTS

Patient Characteristics

Of 91 patients, 63 had chronic AF and the remaining 28 had paroxysmal AF at the time of the echocardiographic study. Forty-three patients had AoSEC, and 48 patients did not. The clinical profiles of the two patient groups are summarized in Table 1. Patients with AoSEC were older and had a higher prevalence of chronic AF and a smoking habit compared with those without AoSEC. No significant difference was found in BP or prevalence of hyperlipidemia. Oral anticoagulant and antiplatelet were similar in the two groups. The intensity of the anticoagulation estimated with the international normalized ratio did not differ between the two groups. Although there was no significant difference in the prevalence of prior cerebral embolism between the two groups, prior symptomatic, peripheral embolism was seen more frequently in patients with AoSEC than in those without AoSEC.

Transthoracic Echocardiographic Measurements

Transthoracic echocardiographic variables are shown in Table 2. Although there was no significant difference in transthoracic echocardiographic dimensions between the two groups, the prevalence of mitral regurgitation was higher in patients with AoSEC than in those without AoSEC.

TEE Findings

TEE variables are shown in Table 3. The LA appendage peak flow velocity was significantly lower in patients with AoSEC than in those without AoSEC, and the grade of LASEC and prevalence of LA thrombi were significantly higher in patients with AoSEC than in those without AoSEC. Although aortic atherosclerotic grade was greater in patients with AoSEC than in those without AoSEC, aortic dimensions did not differ between the two groups.

Hemostatic Markers

Plasma levels of hemostatic markers are summarized in Table 4. Levels of TAT (normal, < 3 ng/mL), D-dimer (normal, < 150 ng/mL), and PIC (normal, < 0.8 μg/mL) were significantly higher in patients with AoSEC. These findings indicated that hypercoagulability along with the increased fibrinolytic state were present in patients with nonrheumatic AF and AoSEC compared with those without AoSEC. In contrast, there was no significant difference in PF4 (normal, < 20 ng/mL) or β-TG level (normal, < 50 ng/mL) between the two groups.

Multiple Logistic Analysis

Table 5 shows the result of multiple logistic analysis of echocardiographic variables related to AoSEC. For this analysis, variables that showed significant differences between the two groups when univariate analyses were included as explanatory variables. Mitral regurgitation, LASEC, and aortic atherosclerosis were independently predictive of AoSEC. However, LA thrombi showed a borderline

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**Table 1—Baseline Clinical Characteristics in the Two Patient Groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With AoSEC (n = 43)</th>
<th>Without AoSEC (n = 48)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34 (79)</td>
<td>34 (71)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>72 ± 2</td>
<td>68 ± 1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Chronic AF</td>
<td>38 (88)</td>
<td>25 (52)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>120 ± 2</td>
<td>122 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (35)</td>
<td>12 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (9)</td>
<td>7 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>24 (56)</td>
<td>17 (35)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Warfarin</td>
<td>29 (67)</td>
<td>31 (66)</td>
<td>NS</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.70 ± 0.11</td>
<td>1.77 ± 0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>15 (35)</td>
<td>17 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>History of embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral arteries</td>
<td>10 (23)</td>
<td>14 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral arteries</td>
<td>4 (10)</td>
<td>0 (0)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE or No. (%) of patients; PT-INR = prothrombin time-international normalized ratio; NS = not significant.

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**Table 2—Transthoracic Echocardiographic Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>With AoSEC (n = 43)</th>
<th>Without AoSEC (n = 48)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA dimension, mm</td>
<td>46 ± 2</td>
<td>43 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular dimension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastole, mm</td>
<td>53 ± 1</td>
<td>51 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>End-systole, mm</td>
<td>36 ± 2</td>
<td>36 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation, %</td>
<td>10 (23)</td>
<td>4 (8)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE or No. (%) of patients; see Table 1 for expansion of abbreviation.
associated with low shear rate and thereby promoted formation of SEC.6 AF itself also could decrease the forward flow and could be involved in the formation of AoSEC4; therefore, patients in sinus rhythm at the time of the TEE study were excluded from the present analysis. Most patients with paroxysmal AF who were in sinus rhythm at the time of the TEE study did not have AoSEC or increased levels of hemostatic markers.

Aortic atherosclerosis and LASEC were independently associated with AoSEC, but there was no significant relation between aortic atherosclerosis and LASEC. An atherosclerotic aorta might produce localized turbulence and blood stasis in addition to endothelial damage and might thereby facilitate formation of SEC. A larger aortic dimension would reduce the shear rate and would thereby promote SEC formation in the aorta6; however, aortic dimensions did not differ between patients with and without AoSEC in the present study.

Mitral regurgitation is known to prevent SEC formation in the LA by turbulent, regurgitant flow into the LA20–22; however, forward blood flow would be reduced in the presence of mitral regurgitation, and SEC formation could be promoted in the aorta as shown in the present study. Indeed, AoSEC disappeared after mitral valve replacement in one patient reported by Zainea et al.5 The effect of mitral regurgitation on the formation of SEC is, therefore, opposite in the LA and in the thoracic aorta. Clinically, mitral regurgitation is associated with reduced embolic events,21 and LASEC could be a better predictor for stroke.

SEC in the Thoracic Aorta

The mechanisms of formation of AoSEC appeared to be similar to those of LASEC. Among them were low shear rate, hyperfibrinogenemia, and others.4,6,19 Larger chamber dimensions and low flow rate were associated with low shear rate and thereby promoted the appearance of SEC.6 AF itself also could decrease the forward flow and could be involved in the formation of AoSEC4; therefore, patients in sinus rhythm at the time of the TEE study were excluded from the present analysis. Most patients with paroxysmal AF who were in sinus rhythm at the time of the TEE study did not have AoSEC or increased levels of hemostatic markers.

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SEC in the thoracic aorta appears to be a marker for increased morbidity and mortality.6,19,23–25 Stroke Prevention in Atrial Fibrillation investigators showed that complex aortic plaque was a risk for thromboembolism in addition to LA appendage dysfunction.7 In the present study, the prevalence of cerebral embolism did not differ between patients with and without AoSEC; however, embolism of the peripheral arteries was observed exclusively in patients with AoSEC. The higher prevalence of cerebral embolism, similarly seen in both study groups, might be attributable to patient selection of the present study.

#### Table 4—Plasma Levels of Hemostatic Markers*

<table>
<thead>
<tr>
<th>Variables</th>
<th>With AoSEC (n = 43)</th>
<th>Without AoSEC (n = 48)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF4, ng/mL</td>
<td>24.8 ± 4.5</td>
<td>20.2 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>β-TG, ng/mL</td>
<td>84.2 ± 8.6</td>
<td>75.6 ± 7.6</td>
<td>NS</td>
</tr>
<tr>
<td>TAT, ng/mL</td>
<td>9.6 ± 1.7</td>
<td>5.5 ± 0.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>D-dimer, ng/mL</td>
<td>193.7 ± 24.9</td>
<td>119.2 ± 12.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>PIC, μg/mL</td>
<td>1.3 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE; see Table 1 for expansion of abbreviation.

#### Table 5—Multiple Logistic Analysis of Echocardiographic Variables Related to AoSEC*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral regurgitation</td>
<td>7.53</td>
<td>1.33–42.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Low LA appendage flow</td>
<td>0.99</td>
<td>0.96–1.03</td>
<td>0.69</td>
</tr>
<tr>
<td>LASEC</td>
<td>2.14</td>
<td>1.16–3.94</td>
<td>0.02</td>
</tr>
<tr>
<td>LA thrombi</td>
<td>50.31</td>
<td>8.51–351.13</td>
<td>0.07</td>
</tr>
<tr>
<td>Aortic atherosclerosis</td>
<td>1.85</td>
<td>1.02–3.42</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*CI = confidence interval.

Discussion

The major findings of the present study are as follows. First, AoSEC was found in nearly one half of the relatively older patients who had AF at the time of the TEE study. Mitral regurgitation, LASEC, and aortic atherosclerotic grade emerged as independent predictors of AoSEC. Second, patients with AoSEC showed increased levels of coagulation and fibrinolysis compared with those without AoSEC. Platelet activity did not differ between the two groups. Interestingly, embolism of the peripheral arteries was seen more frequently in patients with AoSEC than in those without AoSEC.

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Hemostatic Markers

In patients with nonrheumatic AF, the levels of several hemostatic markers increased when compared with the levels of control subjects in sinus rhythm.\textsuperscript{5,13,26} It remains controversial whether platelet function is activated in patients with AF.\textsuperscript{9,10,13} Patients with AF who had additional abnormalities, including LA thrombi or decreased flow velocity in the LA appendage, showed an increased coagulation level and fibrinolytic state compared with those with AF but without these additional abnormalities.\textsuperscript{11,12}

However, it remains to be elucidated whether patients with AF and AoSEC have increased levels of hemostatic markers. In the present study, patients with AF complicated with AoSEC had increased levels of coagulation and fibrinolysis compared with those with AF but without AoSEC. AoSEC, occurring in a low shear state and hypercoagulable environment, could predispose to microthrombi, thus activating the endogenous thrombotic system. The mean TAT level in patients without AoSEC exceeded the normal range, suggesting that the coagulation system might also be activated in this patient group. The β-TG level exceeded the normal range in patient groups with and without AoSEC, but PF4 remained at approximately the borderline level. We could not provide a plausible explanation for the elevated β-TG level; nevertheless, platelet activity did not differ between the two groups.

These findings indicated that patients with AF who have AoSEC could actually be in the prothrombotic state, and more intense anticoagulation might be merited in these patients. Indeed, anticoagulation with warfarin was effective in reducing the incidence of thromboembolic events in patients with nonrheumatic AF and complex aortic plaque.\textsuperscript{7}

Study Limitations

The findings of the present study are limited for several reasons. First, the levels of hemostatic markers were determined when most patients were receiving oral antithrombotic therapies, either warfarin or antiplatelets. Therefore, hemostatic markers could have been affected by the antithrombotic treatments.\textsuperscript{27,28} The prevalence of patients receiving antithrombotic treatment and intensity of anticoagulation did not differ between patients with and without AoSEC; however, both the coagulation level and fibrinolytic activity were increased in patients with AoSEC when compared with patients without AoSEC. This suggests that patients with AoSEC had increased coagulation levels even with anticoagulation or that the intensity of anticoagulation in the present study (mean international normalized ratio of < 2.0) was simply not high enough to suppress coagulation activity. In Japan, a relatively low intensity of anticoagulation with warfarin (international normalized ratio between 1.5 and 2.1) was accepted for prevention of stroke in patients with AF.\textsuperscript{29}

Second, the prevalence of paroxysmal AF was higher in patients without AoSEC. Although we included patients with chronic and paroxysmal AF who had AF at the time of the TEE study, the higher prevalence of paroxysmal AF could lead to lower levels of hemostatic markers in those patients without AoSEC.\textsuperscript{11} Third, because of the retrospective nature of the present study, we did not have findings concerning the TEE and hemostatic markers at the time of the embolic event. Finally, the number of patients was too small to draw a definitive conclusion. Additional prospective studies on a larger scale of patients are warranted.

Clinical Implications

Although limited for the above-mentioned reasons, the present study suggests that the search for AoSEC in addition to LA appendage dysfunction with TEE could provide valuable information on prothrombotic state in patients with nonrheumatic AF. Patients with nonrheumatic AF complicated with AoSEC could be actually in the prothrombotic state; therefore, intensive anticoagulation with oral warfarin may be merited for these patients.

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REFERENCES


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