Spontaneous Echo Contrast and Hemorheologic Abnormalities in Cerebrovascular Disease

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Background and Purpose  Spontaneous echo contrast (SEC) is thought to represent a risk factor for cardioembolic stroke. In vitro studies suggest that SEC results from interaction between red cells and fibrinogen. To better understand the relation between SEC and stroke and to investigate the in vivo genesis of SEC, we examined the relation between SEC, the constituents of the blood, and plasma and serum viscosity in patients with acute stroke or chronic cerebrovascular disease.

Methods  Fifty patients with acute stroke or chronic cerebrovascular disease referred for transesophageal echocardiogram (TEE) were studied by transthoracic echocardiography and TEE. Complete blood count, fibrinogen, albumin, γ-globulin, and plasma and serum viscosity determinations were made. Left atrial SEC was graded as absent, mild, or marked by means of TEE.

Results  SEC was absent in 31 patients, mild in 10 patients, and marked in 9 patients. Higher grade of SEC was associated with a significantly greater percentage of patients with atrial fibrillation and larger left atrial dimension. Atrial fibrillation was present in 23% of the patients in the SEC absent group, 50% of the patients in the mild SEC group, and 78% of the patients in the marked SEC group (P<.01). Left atrial diameter averaged 3.8±0.6 cm in the SEC absent group, 4.3±1.1 in the mild SEC group, and 4.9±0.7 in the marked SEC group (P<.001). Hematocrit, white blood cell count, and platelet count did not differ among the three groups. Fibrinogen, γ-globulin, plasma viscosity, and serum viscosity values were all significantly higher in the presence of SEC (P<.05). Fibrinogen values were 361±79 mg/dL in the SEC absent group and 427±135 mg/dL in the marked SEC group. γ-Globulin levels were 0.75±0.23 g/dL in the SEC absent group and 1.06±0.48 g/dL in the marked SEC group. Both plasma viscosity (1.97 cp) and serum viscosity (1.64 cp) were higher in the marked SEC group than in the SEC absent group (1.77 and 1.50 cp, respectively).

Conclusions  In patients with acute stroke or chronic cerebrovascular disease, the severity of SEC was not related to albumin, hematocrit, white cell count, or platelet count but rather to elevated fibrinogen levels and concomitant increases in both plasma and serum viscosity. Moreover, increasing grade of SEC was associated with significantly increased left atrial diameter and a higher percentage of patients in atrial fibrillation. (Stroke. 1994;25:1564-1569.)

Key Words  • cardioembolic stroke • echocardiography • erythrocytes • fibrinogen

As seen during echocardiographic examination, spontaneous echo contrast (SEC) appears as a swirling motion or smokelike appearance of blood. Left atrial SEC has gained considerable attention recently because of its reported association with intracardiac thrombus formation and increased thromboembolic risk.1 The pathogenesis of SEC is unclear, but in vitro studies have suggested that SEC is generated by an interaction between red blood cells (RBCs) and plasma proteins in a flow-dependent manner.2,3 When static, RBCs are echogenic, but this echogenicity is abolished when the RBCs are lysed4-5 or vigorously stirred.6-7 In vitro, static blood at a shear rate of zero produces a homogeneous gray echocardiographic image.6 As the shear rate increases, the characteristic swirling waves of SEC are seen until high shear rates SEC disappears altogether.2 The echocardiographic gray scale of SEC in vitro has been related exponentially to the concentration of plasma fibrinogen and the hematocrit.8 The relation between intensity of SEC and hemorheologic factors in vivo is not known. The goal of this study was to determine if the intensity of SEC is related to fibrinogen levels in patients with acute stroke or chronic cerebrovascular disease. We reasoned that the incidence of SEC should be higher in these patients than in those patients without cerebrovascular disease because of previous reports associating SEC with thromboembolic risk.1 Because hematocrit and plasma fibrinogen levels profoundly influence blood viscosity, we examined the relation between SEC, plasma and serum viscosity, and blood composition.

Subjects and Methods

Patients with acute cerebral infarction, transient ischemic attack (TIA), or chronic cerebrovascular disease were prospectively recruited for this study. All subjects gave written informed consent to participate and undergo phlebotomy, transesophageal echocardiography (TEE), and neurological examination. Patients who had experienced an ischemic stroke within the past 7 days were eligible regardless of the putative stroke mechanism, whereas subjects with hemorrhagic stroke or subarachnoid hemorrhage were excluded. Patients with chronic cerebrovascular disease were also recruited if they had two or more known habits or cardiovascular diseases that have
been recognized as stroke risk factors. These clinical risk factors for stroke include prior history of stroke or TIA, hypertension, diabetes mellitus, tobacco use, atrial fibrillation, and ischemic and valvular heart disease. A detailed medical history was obtained on all patients, and results of electrocardiography, carotid ultrasonography, and angiography examinations, when available, were recorded. Stroke mechanism was determined for the stroke and TIA patients based on Stroke Data Bank criteria.8

Fasting morning blood samples were obtained between 8 and 11 AM. Samples were anticoagulated with either the disodium salt of EDTA for complete blood count and plasma viscosity determinations or diluted 9:1 by volume in a solution of 3.8% sodium citrate for fibrinogen determination. Samples were collected without anticoagulant for serum chemistry and serum viscosity measurements. Plasma and serum viscosities were measured at 25°C by Ostwald viscometry in a microviscometer (Cannon Instrument Co) as described previously.9,10 The clinical pathology department of Oregon Health Sciences University performed the complete blood count with the S Plus IV Coulter Counter (Coulter Corp), the serum chemistries with a 737 analyzer (Hitachi Scientific Instruments), fibrinogen concentration by the modified thrombin clotting time, and γ-globulin by serum protein electrophoresis.

Most patients were examined by transthoracic echocardiography (TTE), and all patients were examined by TEE. TTE and Doppler (color-flow, pulsed-wave, and when appropriate, continuous-wave) examinations were performed with 2.5-MHz or 3.5-MHz transducers with a Hewlett-Packard Sonos 1000 imaging system. TEE examinations were performed with a Hewlett-Packard model 21362A transesophageal imaging transducer. All TTE and TEE studies were recorded on VHS videotape and later reviewed. Left atrial diameter and left ventricular measurements were made from the parasternal long-axis view by use of standard methods.12 TEE left atrial dimensions were measured in two dimensions.13 The sagittal axis dimension (anteroposterior dimension) was measured from the coaptation point of the closed mitral leaflets at a 90° angle to the plane of the mitral valve up to the posterior left atrial wall.13 The frontal axis dimension (lateral dimension) was measured at half of the sagittal axis dimension from the lateral to medial wall (atrial septum) parallel to the mitral valve plane.13

TEE studies were reviewed independently in a blinded fashion by two echocardiographers for the presence and grade of SEC, left atrial size, function, and thrombus. When the results differed between these two echocardiographers, a third echocardiographer independently reviewed the study. The interpretation of the third echocardiographer was considered final. Left atrial thrombus was diagnosed if any intracavity echo density with irregular margins, either in continuity with or separate from the endocardium of the left atrium or left atrial appendage, was seen. Left ventricular thrombus was identified if any intracavitary echo density with irregular margins, either in continuity with or separate from the endocardium of the left ventricle in an area of abnormal wall motion, was seen. Left atrial SEC was defined as a dynamic smokelike appearance of blood with the characteristic swirling pattern. When the presence of SEC was suspected, the gain settings were decreased in a stepwise fashion to exclude white noise artifact due to excessive gain. SEC was graded on a three-point scale as absent, mild, or marked based on its appearance at a normal gain control setting.1 SEC was graded as mild if echo contrast was visible in some portion of the left atrium or marked if echo contrast was intense and appeared throughout the left atrium. Summary statistics (mean and SD) were calculated for each continuous variable. Frequency data were summarized by expressing the variable as a percentage, and significance was assessed by χ². Data are expressed as mean ± SD. Groups were compared by means of ANOVA with the Bonferroni correction for multiple comparisons. Agreement between the two echocardiographers for rating the severity of SEC was evaluated using κ.14,15 A κ of 1 indicates perfect agreement; a κ of 0 indicates only chance agreement between two observers.15 In general, values >0.75 indicate excellent agreement, values of 0.4 to 0.75 indicate good agreement, and values <0.4 indicate marginal agreement.15

### Table 1. Selected Population Demographic Parameters and Grade of Spontaneous Echo Contrast

<table>
<thead>
<tr>
<th>Grade of SEC</th>
<th>No. of patients</th>
<th>Absent</th>
<th>Mild</th>
<th>Marked</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>31</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64±5</td>
<td>68±5</td>
<td>68±6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>84%</td>
<td>100%</td>
<td>88%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>23%</td>
<td>20%</td>
<td>22%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>68%</td>
<td>20%</td>
<td>67%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>20%</td>
<td>30%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>43%</td>
<td>30%</td>
<td>89%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>36%</td>
<td>40%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac history
- Coronary artery disease: 52% (50% 67%) NS
- Congestive heart failure: 7% (20% 22%) NS
- Prior stroke: 31% (20% 22%) NS
- Prior TIA: 19% (10% 11%) NS

Status at time of enrollment
- Acute cerebral infarct: 90% (60% 78%) NS
- Acute TIA: 0% (10% 11%) NS
- Chronic cerebrovascular disease: 10% (30% 11%) NS

SEC indicates spontaneous echo contrast; TIA, transient ischemic attack.

*χ² test.

Results

There was agreement between the two echocardiographers for the presence and grade of SEC in 47 of 50 TEE studies. In two studies the echocardiographers disagreed on the distinction between absent and mild SEC. The third echocardiographer classified one study as SEC absent and one as mild SEC. In grading the remaining study there was disagreement in differentiating between mild and marked SEC. The third echocardiographer classified this study as mild SEC. The overall κ was 0.89, indicating excellent agreement beyond chance between the two echocardiographers.

Selected demographic data are shown in Table 1. SEC was present in 19 of the 50 patients studied (38%). Of 19 patients with SEC, 10 patients had mild and 9 marked SEC. The majority of the patients were male, with mean age ranging from 64 years in the SEC absent group to 68 years in the marked SEC group. There were no significant differences in age, sex, history of smoking, diabetes, hypertension, or coronary artery disease between the patients with or without SEC. More subjects with mild and marked SEC had a clinical history of congestive heart failure than patients without SEC.
TABLE 2. Distribution of Cardiac Rhythm and Echocardiographic Parameters by Grade of Spontaneous Echo Contrast

<table>
<thead>
<tr>
<th>Grade of SEC</th>
<th>Absent</th>
<th>Mild</th>
<th>Marked</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac rhythm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>77%</td>
<td>50%</td>
<td>22%</td>
<td>.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>23%</td>
<td>50%</td>
<td>78%†</td>
<td></td>
</tr>
<tr>
<td>Left atrial dimension, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasternal long axis</td>
<td>3.8±0.6</td>
<td>4.3±1.1</td>
<td>4.9±0.7†</td>
<td>.0001</td>
</tr>
<tr>
<td>Anterior-posterior</td>
<td>4.7±1.0</td>
<td>5.1±1.3</td>
<td>6.1±1.6†</td>
<td>.01</td>
</tr>
<tr>
<td>Transverse</td>
<td>4.5±1.1</td>
<td>5.4±1.3</td>
<td>5.5±1.6†</td>
<td>.0001</td>
</tr>
<tr>
<td>Left ventricular diastolic dimension, cm</td>
<td>4.5±0.7</td>
<td>5.6±1.4†</td>
<td>5.2±1.2</td>
<td>.01</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>23±10</td>
<td>17±7</td>
<td>17±7</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral insufficiency severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>25%</td>
<td>10%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>65%</td>
<td>50%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>10%</td>
<td>20%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0%</td>
<td>20%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>No. of thrombi seen</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Location</td>
<td>LV</td>
<td>LV</td>
<td>LA</td>
<td></td>
</tr>
</tbody>
</table>

SEC indicates spontaneous echo contrast; LV, left ventricle; LA, left atrium.
*ANOVA or \( \chi^2 \) test.
†Significant difference compared with patients with SEC absent by post hoc Student-Newman-Keuls test.

Forty-one patients presented with acute cerebral infarction, 2 patients with recent TIAIs, and 7 with remote stroke, TIA, or syncope. Overall, 14 patients had a history of previous stroke, and 8 patients had a previous TIA. The incidence of SEC in these 22 patients was 27% (6/22). Of the 41 subjects with acute stroke, 24% experienced symptoms related to atherothrombotic mechanism, 42% experienced cardioembolic stroke, and 32% lacunar infarction. In the remaining patient (2%) the presumed cause of cerebral ischemic symptoms could not be determined. SEC was observed in 8 of 17 (47%) of subjects with cardioembolic stroke compared with 2 of 10 patients (20%) with atherothrombotic and 3 of 13 (23%) with lacunar mechanisms. Of the 7 acute stroke patients with marked SEC, all but 1 experienced stroke as a result of cardioembolism.

The relations between heart rhythm, echocardiographic findings, and grade of SEC are illustrated in Table 2. The number of patients with atrial fibrillation increased with higher grade of SEC. Only 23% of patients in the SEC absent group were in atrial fibrillation, whereas 50% of the patients in the mild SEC group and 78% of the patients in the marked SEC group were in atrial fibrillation at the time of the TEE exam. Left atrial chamber size measured by TTE or TEE was larger with increasing grade of SEC. In the parasternal long-axis view, mean left atrial chamber diameter was 3.8±0.6 cm for the SEC absent group, 4.3±1.1 cm for the mild SEC group, and 4.9±0.7 cm for the marked SEC group. Transesophageal mid left atrial anteroposterior and frontal (longitudinal) end-systolic dimensions were 4.7±1.0x4.5±1.0 cm for the SEC absent group, 5.1±1.3×5.4±1.3 cm for the mild SEC group, and 6.1±1.6x6.5±1.6 cm for the marked SEC group. The left ventricle was also larger with increasing grade of SEC. Mean transthoracic parasternal long-axis end-diastolic diameters were 4.5±0.7 cm for the SEC absent group, 5.6±1.4 cm for the mild SEC group, and 5.2±1.2 cm for the marked SEC group. Left ventricular systolic function as assessed by mean fractional shortening was 23±10% for the SEC absent group, 17±7% for the mild SEC group, and 17±7% for the marked SEC group. There was no consistent relation between the severity of mitral insufficiency and the grade of SEC. Three intracardiac thrombi were identified: a left atrial appendage thrombus was found in the marked SEC group, and left ventricular mural thrombi were seen in both the SEC absent and mild SEC groups.

The relations between blood composition, viscosity parameters, and SEC score are shown in Table 3. Hematocrit, white blood cell count, and platelet count did not differ significantly among the three grades of SEC. Fibrinogen values increased with increasing grade of SEC, from 361±97 mg/dL in the SEC absent group to 423±124 mg/dL in the mild SEC group and 427±135 mg/dL in the marked SEC group. Although this trend was not statistically significant when the three groups were compared and corrected for multiple comparisons, when fibrinogen levels were evaluated simply as SEC absent (361±97 mg/dL) or present (425±125 mg/dL) the difference was significant (P<.05). \( \gamma \)-Globulin levels, as well as plasma and serum viscosity, rose with increasing grade of SEC. \( \gamma \)-Globulin values rose from 0.75±0.23 g/dL in the SEC absent group to 1.04±0.57 g/dL in the mild SEC group and to 1.06±0.48 g/dL in the marked SEC group. These differences were not
Between SEC and left atrial enlargement. Other investigators have also shown a strong association by similar hemorheologic forces. We found that the presence of SEC may be related to left atrial dimension. In vitro experiments have shown that SEC is generated by an interaction between RBCs and plasma proteins and depends on flow rate and shear. Besides RBC aggregation, platelet activation has been suggested as a cause of SEC. This explanation is unlikely because flow-induced platelet activation usually requires a very high rather than a low shear rate. Nevertheless, these observations are consistent with the hypothesis that SEC is more frequently associated with cardiac abnormalities, resulting in low-flow states. Cardiac dysfunction, including enlargement of the left atrium and left ventricle, decreases the shear forces within the left atrium, thereby promoting RBC aggregation. Likewise, elevated plasma viscosity resulting from an increased concentration of fibrinogen, immunoglobulins, and other large protein molecules such as macroglobulins promotes RBC aggregation, especially at low rates of shear. In the present study we found a strong link between the grade of SEC and elevated plasma and serum viscosity in patients with acute stroke or chronic cerebrovascular disease.

Because fibrinogen is essential to the genesis of SEC in vitro and is the principal determinant of plasma viscosity, it is logical to expect that plasma viscosity would be elevated in patients with SEC. In patients with nonvalvular atrial fibrillation, Black and associates found higher concentrations of fibrinogen in patients with SEC than in patients without SEC. We also found higher concentrations of fibrinogen in patients with SEC than in patients without SEC. However, despite the highly significant differences in plasma viscosity among the three groups, only when SEC was considered as either present or absent was the between-group difference in fibrinogen levels significant (361 ± 97 mg/dL in the SEC absent group versus 425 ± 125 mg/dL in the SEC present group; P<.05). This observation suggests that blood proteins in addition to fibrinogen may contribute to serum viscosity and to the genesis of SEC in vivo. One potential contributor to increased plasma viscosity is the concentration of γ-globulin. When SEC was considered as either present or absent, γ-globulin levels were significantly higher in the SEC present group (1.97 ± 0.17 cp; P<.01) compared with the SEC absent group (1.50 ± 0.08 cp).

### Discussion

Although a uniform standard for grading SEC has not been established, other investigators have graded the severity of SEC on a three-point scale as absent, mild, and marked (severe). However, the reproducibility of grading SEC by two echocardiographers using this three-point scale has not been reported previously. Because data analysis in the present study was based on the presence and severity of SEC, it was important to show that two echocardiographers could reliably grade the severity of SEC. The overall κ of 0.89 for the grading of SEC indicates excellent agreement and demonstrates that SEC can be reliably detected and graded as absent, mild, or marked. In vivo experiments have shown that SEC is generated by an interaction between RBCs and plasma proteins and depends on flow rate and shear. The results of our study suggest that SEC in vivo is generated by similar hemorheologic forces. We found that the presence of SEC may be related to left atrial dimension. Other investigators have also shown a strong association between SEC and left atrial enlargement. The relation between SEC and left ventricular dysfunction is less consistent. It has been suggested as a cause of SEC. This explanation is unlikely because flow-induced platelet activation usually requires a very high rather than a low shear rate.

### Table 3. Blood Constituents, Viscosity, and Grade of Spontaneous Echo Contrast

<table>
<thead>
<tr>
<th>Blood Constituent</th>
<th>Grade of SEC</th>
<th>Absent (P&lt;NS)</th>
<th>Mild (P&lt;NS)</th>
<th>Marked (P&lt;NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41±4</td>
<td>42±6</td>
<td>43±6</td>
<td></td>
</tr>
<tr>
<td>White blood count, 10³/mL</td>
<td>8.3±2.9</td>
<td>8.0±2.1</td>
<td>9.5±5.0</td>
<td></td>
</tr>
<tr>
<td>Platelet count, 10³/mL</td>
<td>271±125</td>
<td>245±47</td>
<td>238±54</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>361±97</td>
<td>423±124</td>
<td>427±135</td>
<td></td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>3.99±0.40</td>
<td>3.75±0.77</td>
<td>3.89±0.56</td>
<td></td>
</tr>
<tr>
<td>γ-Globulin, g/dL</td>
<td>0.75±0.23</td>
<td>1.04±0.57</td>
<td>1.06±0.48</td>
<td></td>
</tr>
<tr>
<td>Plasma viscosity, cp</td>
<td>1.77±0.14</td>
<td>1.94±0.20</td>
<td>1.97±0.17</td>
<td></td>
</tr>
<tr>
<td>Serum viscosity, cp</td>
<td>1.50±0.06</td>
<td>1.58±0.15</td>
<td>1.64±0.07</td>
<td></td>
</tr>
</tbody>
</table>

SEC indicates spontaneous echo contrast. ANOVA with corrections for multiple comparisons, in comparison with SEC absent group.
potential clinical importance, SEC will remain an area of interest and investigation until these issues are resolved.

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