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 cm in the mild SEC group, and 4.9±0.7 cm 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±97 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.)

Keywords  •  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. 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. When static, RBCs are echogenic, but this echogenicity is abolished when the RBCs are lysed or vigorously stirred. In vitro, static blood at a shear rate of zero produces a homogeneous gray echocardiographic image. As the shear rate increases, the characteristic swirling waves of SEC are seen until at high shear rates SEC disappears altogether. The echocardiographic gray scale of SEC in vitro has been related exponentially to the concentration of plasma fibrinogen and the hematocrit. 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. 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.9-11 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 chemistry with a Hitachi 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 χ and K.14-15 A χ of 1 indicates perfect agreement; a χ 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.14

### Results

There was agreement between the two echocardiographers on 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 K 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.
Forty-one patients presented with acute cerebral infarction, 2 patients with recent TIAs, 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±1.3x5.4±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 6.5±1.6 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). γ-Globulin levels, as well as plasma and serum viscosity, rose with increasing grade of SEC. γ-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
TABLE 3. Blood Constituents, Viscosity, and Grade of Spontaneous Echo Contrast

<table>
<thead>
<tr>
<th>Grade of SEC</th>
<th>Absent (P=NS)</th>
<th>Mild (P=NS)</th>
<th>Marked (P=NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td>41±4</td>
<td>42±6</td>
<td>43±6</td>
</tr>
<tr>
<td>White blood count, 10⁴/mL</td>
<td>8.3±2.9 (P=NS)</td>
<td>8.0±2.1 (P=NS)</td>
<td>9.5±5.0 (P=NS)</td>
</tr>
<tr>
<td>Platelet count, 10⁴/mL</td>
<td>271±128 (P=NS)</td>
<td>245±47 (P=NS)</td>
<td>238±54 (P=NS)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>361±97 (P=NS)</td>
<td>423±124 (P=NS)</td>
<td>427±135 (P=NS)</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>3.99±0.40 (P=NS)</td>
<td>3.75±0.77 (P=NS)</td>
<td>3.89±0.56 (P=NS)</td>
</tr>
<tr>
<td>γ-Globulin, g/dL</td>
<td>0.75±0.23 (P=NS)</td>
<td>1.04±0.57 (P=NS)</td>
<td>1.06±0.48 (P=NS)</td>
</tr>
<tr>
<td>Plasma viscosity, cp</td>
<td>1.77±0.14 (P&lt;0.02)*</td>
<td>1.94±0.20 (P&lt;0.01)*</td>
<td>1.97±0.17 (P&lt;0.01)*</td>
</tr>
<tr>
<td>Serum viscosity, cp</td>
<td>1.50±0.08 (P&lt;0.002)*</td>
<td>1.58±0.15 (P&lt;0.002)*</td>
<td>1.64±0.07 (P&lt;0.002)*</td>
</tr>
</tbody>
</table>

SEC indicates spontaneous echo contrast. ANOVA with corrections for multiple comparisons, in comparison with SEC absent group.

Statistically significant when corrected for graded SEC, but γ-globulin levels were significantly higher in the combined SEC present groups (1.05±0.51 g/dL) than in the SEC absent group (0.75±0.23 g/dL; P<0.01). Plasma viscosity was significantly elevated in the mild (1.94±0.20 cp; P<0.02) and marked (1.97±0.17 cp; P<0.01) SEC groups in comparison with the SEC absent group (1.77±0.14 cp). Likewise, serum viscosity was greater in the mild (1.58±0.15 cp; P=NS) and marked SEC groups (1.64±0.07 cp; P<0.002) 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 vitro 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. In the present study age, left ventricular diastolic dimension, and fractional shortening were less strongly related to the presence of SEC. 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 this 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<0.05). 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 (1.05±0.51 g/dL) than in the SEC absent group (0.75±0.23 g/dL; P<0.01). Similarly, serum viscosity was elevated in the presence of SEC. Taken together, these findings are consistent with the hypothesis that left atrial SEC is produced by interaction between RBCs and blood proteins that are known to promote RBC aggregation. Both previous in vitro studies and the results of this in vivo study support this view. Studies by others have demonstrated that SEC usually occurs in conjunction with reduced blood flow, which suggests that SEC likely represents blood stasis. Gentle agitation of whole blood in vitro, which disrupts RBC rouleaux formation, easily eliminates SEC. Some mechanisms may operate in vivo. For example, others have suggested that moderate and severe mitral regurgitation have a stirring effect on blood in the left atrium, thereby reducing SEC and thrombus formation. Although there was no statistically significant relationship between grade of SEC and severity of mitral regurgitation in this study, mild mitral regurgitation was more common than moderate or severe regurgitation in all three groups (Table 2).

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
...motion environment. Moreover, although platelet aggregates may exhibit phenomena that approximate SEC, in vitro studies by Merino and colleagues indicate that SEC is generated by a flow-dependent interaction between RBCs and plasma proteins that does not depend on the presence of platelets. Interestingly, SEC is documented in anticoagulated patients and may persist despite the administration of anticoagulants such as heparin and warfarin. Antiplatelet agents, including dipyridamole and aspirin, have no relation between the presence or absence of SEC and anticoagulation or antiplatelet therapy in this study. Turakhia and coworkers related SEC to an exponential function of fibrinogen concentration and hematocrit but not to leukocyte count, platelet count, or serum protein levels. Although not echogenic itself, fibrinogen appears to be a key element in the genesis of SEC. Besides the probable important role of fibrinogen in the genesis of SEC in vivo, elevated fibrinogen is recognized as an important risk factor for stroke, as well as for myocardial infarction. A recent report described significantly increased RBC aggregability in acute stroke and demonstrated RBC hyperaggregability to be a feature of chronic occlusive cerebrovascular disease. In particular, RBC aggregability in stroke subjects was significantly correlated with circulating levels of fibrinogen and globulins and inversely correlated with the albumin-globulin ratio.

Although SEC was observed in 38% of the entire study group, almost two thirds of patients with marked SEC suffered stroke by a cardioembolic mechanism. SEC was more than twice as prevalent among patients with cardioembolic stroke compared with those with stroke from other causes. These findings are similar to those of Albers and coworkers, who found SEC in 45% of patients considered to have stroke by a cardioembolic mechanism. Our results are complementary to a recent report by Chimowitz and associates, who, in a retrospective study found a 21% incidence of stroke among 42 patients with SEC and a 3% incidence of stroke in a control group of 40 patients. That difference was not observed in each of our patients with a cardioembolic stroke reflects the diversity of intracardiac pathologies that may produce cardioembolic events. We suggest that SEC is particularly associated with cardiac findings that promote thrombus formation within the left atrium. Since SEC was observed in some patients without presumed cardioembolic stroke, it is possible that SEC is also a marker of risk for other types of brain infarction. Cardiac abnormalities that result in decreased flow coupled with blood hyperviscosity could contribute to ischemic stroke mechanisms within preclinical arteries and intracerebral arterioles.

Understanding the genesis of SEC may provide insight into the causes and treatment of cardioembolic events. Our study indicates a probable role for fibrinogen in the genesis of SEC in vivo; fibrinogen may thus be an important risk factor for cardioembolism. Our data also indicate that in patients with acute stroke or chronic cerebrovascular disease other serum proteins may contribute to increased serum viscosity and to RBC aggregability, and in turn to SEC in vivo. Regardless of the mechanism of the genesis of SEC, because of its potential clinical importance, SEC will remain an area of interest and investigation until these issues are resolved.

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