Left Atrial Spontaneous Echo Contrast Is Highly Associated With Previous Stroke in Patients With Atrial Fibrillation or Mitral Stenosis

Marc I. Chimowitz, MB, ChB; Michael A. DeGeorgia, MD; R. Michael Poole, MD; Anne Hepner, MD; William M. Armstrong, MD

Background and Purpose: Spontaneous echo contrast is a dynamic smokelike signal that is detected by transesophageal echocardiography in patients with stasis of blood in the left atrium. We designed this study to determine if spontaneous echo contrast is associated with an increased risk of previous stroke or peripheral embolism.

Methods: Forty-two patients with spontaneous echo contrast were identified (34 had atrial fibrillation or mitral stenosis; 8 had neither). Control subjects comprised 40 patients randomly selected from patients with atrial fibrillation or mitral stenosis who did not have spontaneous echo contrast at transesophageal echocardiography. The frequency of vascular risk factors, echocardiographic features, and stroke or peripheral embolism within 1 year of echocardiography were compared in the two groups.

Results: The frequency of traditional risk factors for stroke were the same in both groups, yet 9 of 42 patients with spontaneous contrast had stroke or peripheral embolism compared with only 1 of 40 control subjects ($P<.02$; relative risk, 10.6; 95% confidence interval, 1.3 to 88.4). In patients with nonvalvular atrial fibrillation, 6 of 12 patients with spontaneous contrast had a stroke or peripheral embolism compared with 1 of 28 patients without spontaneous contrast ($P<.001$; relative risk, 27.8; 95% confidence interval, 2.7 to 267.8).

Conclusions: Spontaneous echo contrast is highly associated with previous stroke or peripheral embolism in patients with atrial fibrillation or mitral stenosis. Transesophageal echocardiography may enable stratification of cardioembolic risk in patients with nonvalvular atrial fibrillation. (Stroke 1993;24:1015-1019)

Key Words • atrial fibrillation • cerebrovascular disorders • echocardiography

Left atrial spontaneous echo contrast (SEC) is a dynamic smokelike signal that is detected by transesophageal echocardiography (TEE) in patients with stasis of blood in the left atrium. The most common conditions predisposing to left atrial SEC are atrial fibrillation (AF) and mitral stenosis.1-3 Studies in dogs indicate that SEC represents intracardiac erythrocyte or platelet microaggregates,4-6 which suggests that SEC may be a precursor of thrombus. These findings have prompted studies to determine the association of SEC and previous stroke or peripheral embolism.2,3,7-11

These studies suggest that left atrial SEC is associated with an increased risk of previous stroke; however, traditional risk factors for stroke were not evaluated systematically in any of these studies. Furthermore, the control groups in most of these studies included patients at low risk for thromboembolism, and the results of brain and cerebrovascular imaging in patients with stroke and SEC were not described.

The aims of this study were (1) to determine if left atrial SEC is associated with an increased risk of previous stroke or peripheral embolism independent of vascular and echocardiographic risk factors for thromboembolism and (2) to describe the results of brain and cerebrovascular imaging in patients with stroke and SEC.

Subjects and Methods

Patient Selection

The echocardiographic reports of 648 consecutive patients undergoing TEE at the University of Michigan Medical Center between January 1990 and December 1991 were reviewed for evidence of left atrial SEC. Fifty patients with left atrial SEC were identified: 34 had AF or mitral stenosis, 8 had neither AF nor mitral stenosis, and 8 had a mitral prosthetic valve. The patients with a mitral prosthetic valve were excluded from further analysis. The control group comprised 40 patients with...
native mitral valves randomly selected from 101 patients with AF or mitral stenosis who did not have left atrial SEC at TEE.

**Echocardiography**

TEE was performed using either an Ultramark 9 system (ATL, Bothell, Wash) equipped with a 5-MHz biplane transesophageal probe or a 128XP system (Acuson, Mountain View, Calif) equipped with a 5-MHz monoplane transesophageal probe. SEC was identified as a dynamic smokelike signal that swirled slowly in a circular pattern in the left atrium. The presence of SEC was confirmed by decreasing the gain settings to exclude background noise artifact. We relied on the evaluation of a single echocardiographer (W.M.A.) to determine the presence of SEC because the interobserver variability for the diagnosis of SEC is extremely low, ie, in the range of 1.9% to 2.5%.8,11

Echocardiographic features other than SEC that were evaluated were left ventricular function, left ventricular hypertrophy, left atrial diameter, the structure and function of all valves, and the presence of left atrial thrombus. Left ventricular function was classified as normal or mildly, moderately, or severely depressed. Left atrial diameter was obtained by measuring the largest diameter of the left atrium in the four-chamber view. Mitral regurgitation was graded using a semiquantitative scale (from 0 to +3) based on color flow imaging.

**Clinical Features and Stroke Evaluation**

The medical records of all patients were reviewed to determine the following clinical features: age; serum cholesterol; history of hypertension, diabetes, smoking, prior myocardial infarction, cardiomyopathy, or congestive heart failure; previous anticoagulant or antiplatelet therapy; and ischemic stroke or peripheral embolism within 1 year of TEE. Ischemic stroke was defined by the presence of a focal neurological deficit that was sudden in onset, persistent, and associated with a cerebral infarction on brain imaging. Brain and vascular imaging studies of patients who had suffered an ischemic stroke were reviewed to determine the location, number, and size of cerebral infarcts and the presence of large artery occlusive disease proximal to the infarcts.

**Statistical Analysis**

Two statistical analyses were performed. In the primary analysis, patients with left atrial SEC were compared with patients without SEC regarding the frequency of previous stroke or peripheral embolism, vascular risk factors, and echocardiographic features. In a secondary analysis, patients with previous stroke or peripheral embolism were compared with patients without stroke or embolism regarding the presence of SEC, other echocardiographic features, and vascular risk factors. \( \chi^2 \) or Fisher's exact tests were used for categorical variables, and unpaired \( t \) tests were used for continuous variables. All tests were two tailed, and significant levels were defined as \( P<.05 \). Relative risk was estimated by the odds ratio, and 95% confidence intervals were calculated using a Taylor series expansion to approximate variance.12

<table>
<thead>
<tr>
<th>Table 1. Patients With Left Atrial Spontaneous Echo Contrast Versus Patients Without Left Atrial Spontaneous Echo Contrast</th>
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</thead>
<tbody>
<tr>
<td>Clinical/echocardiographic feature</td>
</tr>
<tr>
<td>Mean age (y)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Ever smoked</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Cholesterol &gt;240 mg/dL</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>History of congestive heart failure</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Stroke or peripheral embolism</td>
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<tr>
<td>Antithrombotic therapy†</td>
</tr>
<tr>
<td>Severe mitral regurgitation</td>
</tr>
<tr>
<td>Left ventricular dysfunction‡</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>Left atrial thrombus</td>
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<td>Left atrial size (mm)</td>
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</table>

SEC+, left atrial spontaneous echo contrast present; SEC−, left atrial spontaneous echo contrast absent. Values are mean±SD for age and left atrial size.

*Significant at \( P<0.05 \).
†Warfarin or aspirin.
‡Mild, moderate, or severe.

**Results**

**Patients With SEC Versus Patients Without SEC**

The frequency of stroke or peripheral embolism within 1 year of TEE, stroke risk factors, and echocardiographic features in patients with SEC and in patients without SEC are shown in Table 1. The rates of traditional risk factors for stroke were the same in both groups, yet 9 (21%) of 42 patients with left atrial SEC had a stroke (7 patients) or peripheral embolism (2 patients) compared with only 1 (3%) of 40 patients without SEC (\( P<.02 \); relative risk, 10.6; 95% confidence interval, 1.3 to 88.4). All strokes and peripheral embolism in both groups occurred within 6 weeks of TEE.

The frequency of two echocardiographic features was significantly different (\( P<.05 \)) in the two groups. Mean left atrial size was significantly larger in patients with left atrial SEC, and severe mitral regurgitation was significantly more common in patients without left atrial SEC. Left ventricular dysfunction tended to be more common in patients with SEC (\( P=.05 \)). The frequency of left atrial thrombus was not different in the two groups.

The frequency of the underlying cardiac abnormalities in patients with SEC and in patients without SEC is shown in Table 2. The group without SEC had a higher percentage of patients with nonvalvular AF, and the group with SEC had a higher percentage of patients with valvular AF (ie, AF and mitral stenosis). Of 9 patients with SEC who had a stroke or peripheral embolism, 6 had nonvalvular AF, 1 had mitral stenosis and AF, and 2 had dilated cardiomyopathy without AF or mitral stenosis. The only patient without SEC who
had a stroke had nonvalvular AF. A subgroup analysis of patients with nonvalvular AF showed that 6 (50%) of 12 patients with left atrial SEC had a stroke or peripheral embolism compared with 1 (4%) of 28 patients without SEC (P<.001; relative risk, 27.0; 95% confidence interval, 2.7 to 267.8).

Antithrombotic therapy in patients with SEC and in patients without SEC is shown in Table 2. Twenty-six (62%) of 42 patients with SEC and 20 (50%) of 40 patients without SEC were being treated with either warfarin or aspirin (P=.37). Of 9 patients with SEC who had a stroke or peripheral embolism, 3 were being treated with warfarin, 1 was treated with aspirin, and 5 were treated with neither. Two of the 3 patients treated with warfarin were inadequately anticoagulated at the onset of their thromboembolic events; one patient with nonvalvular AF had a stroke a few days after stopping warfarin treatment in preparation for oral surgery, and another patient with mitral stenosis and AF had a subtherapeutic prothrombin time when he presented with a peripheral embolus. The only patient without SEC who had a stroke had nonvalvular AF and was not taking either warfarin or aspirin.

Patients With Stroke or Peripheral Embolism Versus Patients Without Stroke or Peripheral Embolism

Of 82 patients in this study, 10 had a stroke or peripheral embolism before TEE. A comparison of these 10 patients with 72 patients who had not suffered a stroke or peripheral embolism is shown in Table 3. Patients with stroke were older than patients without stroke, but the difference was not statistically significant. The only factor that was significantly associated with stroke or peripheral embolism was left atrial SEC.
at angiography; the other patient with an infarct in the left posterior cerebral artery distribution had normal transcranial Doppler ultrasound and magnetic resonance angiography of the vertebral, basilar, and posterior cerebral arteries.

Two patients with SEC had peripheral embolism without stroke: one patient had an embolus to the left femoral artery that was followed 6 months later by an embolus to the superior mesenteric artery, and the other patient had an embolus to the right femoral artery.

Discussion

Although SEC can be identified by transthoracic echocardiography,1,13,14 recent studies have shown that SEC is identified more frequently by TEE.7,8,10 In one study of 150 consecutive patients undergoing both procedures, SEC was identified in 29 patients by TEE and in none of the patients by transthoracic echocardiography.10 Studies using TEE suggest that left atrial SEC is associated with atrial fibrillation,3,8,10 mitral stenosis,3 increased left atrial size,26 the absence of mitral regurgitation,2,11 left atrial thrombus,3,8,9,11 and increased thromboembolic risk.3,7,9,11,15

The design of this study differed from previous studies of the association between SEC and prior stroke in the following respects: (1) We evaluated traditional risk factors for stroke. (2) We excluded patients with prosthetic mitral valves. (3) Our control group consisted of patients with AF or mitral stenosis, conditions associated with a high risk of stroke. (4) We analyzed the results of brain and cerebrovascular imaging in patients with stroke to determine if the likely mechanism was cardioembolism.

In the primary analysis comparing patients with and without SEC, we found that left atrial SEC was significantly associated with previous stroke or peripheral embolism, left atrial enlargement, and left ventricular dysfunction (trend only). In addition, severe mitral regurgitation was associated with the absence of SEC. There was some imbalance, however, in the frequency of the underlying cardiac abnormalities in the groups with and without SEC (Table 2). The group without SEC had a higher percentage of patients with nonvalvular AF, and the group with SEC had a higher percentage of patients with valvular AF. These data probably reflect the fact that a minority of patients with nonvalvular AF have SEC,11 whereas patients with coexistent AF and mitral stenosis are more likely to have SEC. The higher frequency of coexistent AF and mitral stenosis in patients with SEC did not correlate directly with the higher rate of thromboembolism in this group: only one of the nine patients with SEC and thromboembolism had coexistent AF and mitral stenosis (Table 2).

In a secondary analysis comparing patients with and without stroke or peripheral embolism, we found that SEC was the only factor associated with stroke or peripheral embolism. However, the power of the study to detect differences in the frequency of some factors (eg, hypertension, myocardial infarction, and severe mitral regurgitation) was low (Table 3).

Although left atrial enlargement was associated with SEC, it was not associated with previous stroke or peripheral embolism. In fact, mean left atrial size was smaller in patients with stroke compared with patients without stroke. Other studies have shown that left atrial enlargement is not associated with an increased risk of stroke in patients with nonvalvular AF.16,17

Severe mitral regurgitation was associated with the absence of left atrial SEC in our study. Most,2,3,11 but not all,10 previous studies of SEC have shown the same result. Presumably, high-flow regurgitant jets of blood from the left ventricle prevent stasis of blood in the left atrium in patients with mitral regurgitation. The association of severe mitral regurgitation and the absence of left atrial SEC suggest the possibility that severe mitral regurgitation may protect against stroke in patients with AF or mitral stenosis. Although we did not find a statistical association between severe mitral regurgitation and the absence of stroke, the power of the study to detect such a difference was low. Of note is that none of the 10 patients who had a stroke or peripheral embolism had severe mitral regurgitation.

Most,3,8,9,11 but not all,10 previous studies have shown that left atrial SEC is associated with left atrial thrombus. We did not find this association: 7 (17%) of 42 patients with SEC and 7 (18%) of 40 patients without SEC in our study had left atrial thrombus. The absence of SEC in patients with thrombus indicates that left atrial thrombus may form in conditions other than those predisposing to SEC. Although the number of patients in this study with left atrial thrombus was relatively low (n=14), our data suggest that previous stroke is more highly associated with left atrial SEC than with left atrial thrombus. One possible explanation for this finding is that SEC may represent a milieu that predisposes to small, soft, fresh thrombi that are more likely to embolize than larger, rigid, and organized thrombi detected at echocardiography.

Previous studies have presumed that the mechanism of stroke in patients with left atrial SEC is cardioembolism. It is possible, however, that stroke in patients with SEC may be caused by mechanisms other than cardioembolism. Patients with nonvalvular AF (who are at risk of having SEC) have a higher incidence of coexistent carotid stenosis than age-matched control subjects without AF.18 A recent study of patients with stroke or transient ischemic attack found that patients with SEC have significantly higher fibrinogen levels than patients without SEC.15 Since elevated fibrinogen is an independent risk factor for stroke,19 patients with SEC and elevated fibrinogen may be at increased risk of both cardioembolic and noncardioembolic stroke.

We cannot provide definite evidence that cardioembolism was the mechanism of stroke in our seven patients with SEC because only two patients underwent vascular imaging. In these two patients, the absence of large artery occlusive disease proximal to large cortical infarcts supports the diagnosis of cardioembolism. In the other five patients who did not undergo vascular imaging, the brain-imaging features suggest that cardioembolism was the likely mechanism of stroke in four of these patients. These features were multiple infarcts in different vascular distributions and wedge-shaped infarcts involving the cerebral cortex.20,21

Although this study was not designed to determine effective therapy for preventing stroke in patients with left atrial SEC, the therapeutic data are of interest (Table 2). Twenty-six (62%) of 42 patients with SEC...
and 20 (50%) of 40 patients without SEC were treated with warfarin or aspirin. Despite more frequent use of antithrombotic therapy in the group with SEC, 9 of 42 patients with SEC had stroke or peripheral embolism compared with 1 of 40 patients without SEC. Analysis of individual cases, however, shows that 7 of the 9 patients with SEC and thromboembolism were not on any antithrombotic therapy or were inadequately anticoagulated. In the 40 patients with AF or mitral stenosis who did not have SEC, 20 (50%) patients were not on any antithrombotic therapy, yet only one of these patients had a previous stroke.

Prospective studies on stroke prevention in patients with nonvalvular AF have recently been published. The results of these studies indicate that warfarin is highly effective for preventing stroke and that aspirin is significantly more effective than placebo, except in patients older than 75 years. Stratification of cardioembolic risk in patients with nonvalvular AF would enable assignment of high-risk patients to warfarin and low-risk patients to aspirin; however, no single vascular risk factor or transthoracic echocardiographic feature emerged as a consistent predictor of increased stroke risk in these prospective studies.

The results of this study and other retrospective studies suggest that TEE may be useful for stratifying cardioembolic risk in patients with nonvalvular AF. In our subgroup analysis of patients with nonvalvular AF, patients with left atrial SEC were 27 times more likely to have had a previous stroke or peripheral embolism than patients without left atrial SEC (95% confidence interval for relative risk, 2.7 to 267.8). Our study population, however, consisted of patients referred for TEE and is probably not representative of a typical cross section of patients with nonvalvular AF. Prospective studies using TEE in nonselected patients are needed to establish definitively that left atrial SEC is a major risk factor for stroke in patients with nonvalvular AF.

References


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