JACC Vol. 21, No. 2
February 1993:451–7

Hematologic Correlates of Left Atrial Spontaneous Echo Contrast and Thromboembolism in Nonvalvular Atrial Fibrillation

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Objectives. **This study examined the relation between left atrial spontaneous echo contrast, hematologic variables and thromboembolism in patients with nonvalvular atrial fibrillation.**

Background. **Left atrial spontaneous echo contrast is associated with left atrial stasis and thromboembolism in patients with nonvalvular atrial fibrillation. However, its hematologic determinants in patients with nonvalvular atrial fibrillation are unknown.**

Methods. **Clinical, hematologic and echocardiographic variables were prospectively measured in 135 consecutive patients with nonvalvular atrial fibrillation undergoing transesophageal echocardiography.**

Results. **Patients with left atrial spontaneous echo contrast (n = 74, 55%) had an increased fibrinogen concentration (p = 0.029), platelet count (p = 0.045), hematocrit (p = NS) and left atrial dimension (p = 0.005). Multivariate analysis showed that left atrial spontaneous echo contrast was independently related to hematocrit (odds ratio = 2.24, p = 0.002), fibrinogen concentration (odds ratio = 2.08, p = 0.008) and left atrial dimension (odds ratio = 1.90, p = 0.004) but not platelet count. It was also associated with left atrial thrombus (n = 15, p = 0.001) and with recent embolism (n = 40, p < 0.001). In 40 clinically stable outpatients without previous embolism, left atrial spontaneous echo contrast was significantly related to hematocrit (p = 0.035), fibrinogen concentration (p = 0.035) and left atrial dimension (p = 0.029) but not to coagulation factor VII, D-dimer, erythrocyte sedimentation rate, platelet count, plasma beta-thromboglobulin, plasma glycocalicin or glycocalicin index.**

Conclusions. **Left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation is independently related to hematocrit, fibrinogen concentration and left atrial dimension, indicating a relatively hypercoagulable state in addition to stasis. These findings support the hypothesis that left atrial spontaneous echo contrast is due to erythrocyte aggregation. Hematologic factors may contribute to its association with thromboembolism.**

(J Am Coll Cardiol 1993;21:451–7)

Recent clinical trials (1) have highlighted the risk of thromboembolism associated with nonvalvular atrial fibrillation. Left atrial spontaneous echo contrast detected by transesophageal echocardiography has been identified as a marker of left atrial thrombus and embolism in this patient group (2). Spontaneous echo contrast refers to smokelike echoes with a characteristic swirling motion distinct from white noise artifact. Previous studies (2,3) have demonstrated an association between left atrial spontaneous echo contrast and conditions favoring stasis of left atrial blood. However, the hematologic determinants of left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation are unknown. We prospectively examined the relation between left atrial spontaneous echo contrast, hematologic variables and thromboembolism in a large consecutive series of patients with nonvalvular atrial fibrillation undergoing transesophageal echocardiography.

Methods

Study patients (Table 1). The study group comprised 135 consecutive patients with nonvalvular atrial fibrillation who underwent transesophageal echocardiography between January and December 1991. Nonvalvular atrial fibrillation was defined as atrial fibrillation at the time of transesophageal echocardiography in the absence of mitral stenosis, moderate or severe mitral regurgitation or a mitral valve prosthesis. Only the initial study was included in patients who also underwent follow-up studies.

There were 93 men and 42 women, with a mean age of 66 ± 11 years (range 24 to 86). Of the 135 patients, 95 underwent transesophageal echocardiography for clinical

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Manuscript received February 5, 1992; revised manuscript received July 25, 1992, accepted July 28, 1992.

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0735-1097/93/$6.00

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Table 1. Characteristics of 135 Patients With Nonvalvular Atrial Fibrillation Related to Left Atrial Spontaneous Echo Contrast

	Left Atrial Spontaneous Echo Contrast		
	Absent (n = 64)	Present (n = 75)	p Value
Embolism	5 (8)	35 (47)	< 0.001
Left atrial thrombus	1 (2)	14 (19)	0.001
Left atrial dimension (mm)	45.4 ± 7.0	48.9 ± 7.1	0.005
Age (yr)	63.8 ± 11.3	68.0 ± 10.5	0.027
Fibrinogen (g/liter)	4.64 ± 1.73	5.27 ± 1.59	0.029
Platelet count (10^9/liter)	230 ± 80	262 ± 98	0.045
Hematocrit (%)	41.3 ± 6.7	42.8 ± 5.1	NS
White cell count (10^9/liter)	6.98 ± 3.01	7.97 ± 2.96	NS
Anticoagulation	21 (34)	26 (35)	NS

Values are expressed as number (%) of patient group or mean ± SD.

indications, including detection of a source of embolism (n = 40), electrical cardioversion (n = 38), endocarditis (n = 6) and miscellaneous (n = 11). There were no intraoperative studies. The 40 patients referred to detect sources of suspected cardiogenic embolism were patients with recent (<1 month) cerebral (n = 30), peripheral (n = 8) or mesenteric (n = 2) embolic events. The origin of atrial fibrillation in these 95 patients included hypertension (n = 30), coronary artery disease (n = 13), postoperative status (n = 9), dilated cardiomyopathy (n = 9), intercurrent medical illness (n = 5), ethanol abuse (n = 4) and miscellaneous causes (n = 9) and was unknown in 16 patients.

The remaining 40 patients were clinically stable outpatients without previous embolism, all receiving aspirin (150 mg/day), who underwent transesophageal echocardiography as part of a research protocol studying nonvalvular atrial fibrillation. Among these 40 outpatients there were 25 men and 15 women, aged 65 ± 10 years (range 35 to 80). The origin of atrial fibrillation in this group included hypertension (n = 9), coronary artery disease (n = 6), dilated cardiomyopathy (n = 4), ethanol abuse (n = 3) and miscellaneous causes (n = 4) and was unknown in 14 patients. This protocol was approved by the Research Ethics Committee of the Eastern Sydney Area Health Service.

Echocardiography. Two-dimensional and Doppler (including color flow mapping) transthoracic echocardiography was performed immediately before transesophageal echocardiography, with a 2.5- or 3.5-MHz imaging transducer (HP77020 AC). Left atrial dimension was determined by standard M-mode criteria (4).

Transesophageal echocardiography was performed with a 5-MHz single-plane (n = 46) or biplane (n = 89) transducer (HP 21362A and HP 21363A). Patients were examined in the fasting state after intravenous sedation with midazolam (1.7 ± 1.1 mg) together with fentanyl (78 ± 21 μg) and pharyngeal anesthesia with topical lidocaine. The presence of left atrial thrombus and spontaneous echo contrast was specifically assessed. Left atrial thrombus was diagnosed by the presence of a clearly defined intracavitary mass, acoustically distinct from underlying endocardium and not due to the pectinate ridges of the atrial appendage (5). Left atrial spontaneous echo contrast was diagnosed by the presence of dynamic smokelike echoes within the left atrial cavity or appendage, with a characteristic swirling motion distinct from white noise artifact (3). The presence or absence of thrombus and spontaneous echo contrast was determined independently by two experienced echocardiographers and any discrepancy was resolved by consensus. Echocardiographic findings were recorded before the availability of hematologic results.

Hematology. Venous blood was drawn without stasis immediately before echocardiography. Hematocrit, fibrinogen concentration, platelet count and white blood cell count were measured in all 135 patients. Hematocrit, platelet count and white blood cell count were measured in a commercial analyzer (Sysmex NE cell counter, TOA Electronics). Fibrinogen concentration was measured with an automated functional assay (6).

The 40 clinically stable outpatients underwent additional hematologic investigations, including erythrocyte sedimentation rate, plasma beta-thromboglobulin, plasma glycocalicin, coagulation Factor VII and D-dimer. Erythrocyte sedimentation rate was determined with the Westergren method. Plasma beta-thromboglobulin, a protein secreted from platelet alpha granules during platelet activation, was measured by radioimmunoassay as previously described (7). Plasma glycocalicin, a fragment of platelet glycoprotein Ib, was measured by an enzyme-linked immunosorbent assay (ELISA) method (8). The glycocalicin index, a dimensionless number calculated as the ratio of the plasma glycocalicin concentration (ng/ml) to the platelet count (10^9/liter) multiplied by 100, is an index of platelet turnover (9). Coagulation Factor VII was measured with an automated analyzer (10). The plasma level of D-dimer, the principal degradation product of cross-linked fibrin, was measured with the Dimertest EIA (AGEN, Brisbane) (11).

Statistical analysis. All data were collected prospectively. The chi-square test or Fisher exact test was used to compare

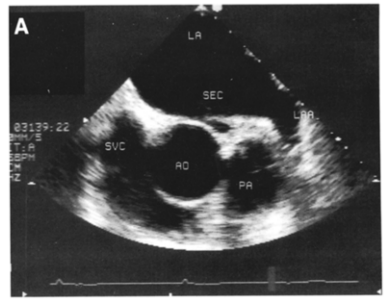
categoric variables. The Student *t* test was used to compare continuous variables, with the exception of erythrocyte sedimentation rate, which was abnormally distributed and was compared with the Mann-Whitney *U* test. Pearson's correlation coefficient was used to evaluate the correlation between continuous variables. Multivariate logistic regression analysis was used to assess the independent relation of variables with left atrial spontaneous echo contrast, embolism and left atrial thrombus. The odds ratios refer to the presence of categoric variables and 1-SD increments in continuous variables and are shown with 95% confidence intervals. Statistical significance was defined as two-tailed $p < 0.05$ and values are reported as mean ± 1 SD.

Results

Hematologic factors and left atrial spontaneous echo contrast. Left atrial spontaneous echo contrast was detected in 74 (55%) of the 135 patients (Fig. 1). The characteristics of patients with and without spontaneous echo contrast are shown in Table 1. In patients with left atrial spontaneous echo contrast, significant increases were found for fibrinogen concentration, platelet count, embolism, left atrial thrombus, left atrial dimension and age. There was a significant negative correlation between hematocrit and fibrinogen concentration ($r = -0.45$, $p < 0.001$). Left atrial dimension did not correlate with either hematocrit ($r = 0.12$, p = NS) or fibrinogen concentration ($r = -0.06$, p = NS).

Multivariate logistic regression analysis was performed with age, anticoagulation, left atrial dimension and all hematologic variables as independent variables (Table 2). Hematocrit, fibrinogen concentration, left atrial dimension and age were independently related to left atrial spontaneous echo contrast. The odds ratios in Table 2 indicate that a 1-SD increase in hematocrit (1 SD = 5.9%) was associated with a twofold increase (odds ratio = 2.24) in the probability of left atrial spontaneous echo contrast. A 1-SD increase in fibrinogen concentration (1 SD = 1.68 g/liter) was also associated with a twofold increase (odds ratio = 2.08) in the probability of left atrial spontaneous echo contrast. Anticoagulation, platelet count and white cell count were not significantly related to spontaneous echo contrast in multivariate analysis.

Embolism and left atrial thrombus. The characteristics of patients with and without recent embolism are shown in Table 3. Patients with recent embolism (n = 40) had a significantly increased prevalence of left atrial spontaneous echo contrast, left atrial thrombus and anticoagulation, increased fibrinogen concentration and increased platelet and white cell count. Multivariate analysis was performed with age, left atrial dimension, all hematologic variables and left atrial spontaneous echo contrast as independent variables. Only spontaneous echo contrast ($p < 0.001$, odds ratio = 9.60 [95% confidence interval 2.84 to 32.38]) and fibrinogen concentration ($p = 0.002$, odds ratio = 2.60 [95% confidence interval 1.42 to 4.77]) were independently related to recent embolism.



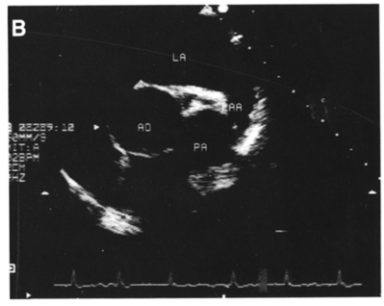


Figure 1. Transesophageal echocardiograms from patients with nonvalvular atrial fibrillation with **(A)** and without **(B)** left atrial spontaneous echo contrast (SEC). AO = aorta; LA = left atrium; LAA = left atrial appendage; PA = pulmonary artery; SVC = superior vena cava.

Left atrial thrombus was detected in 15 (11%) of the 135 patients. All thrombi were located in the left atrial append-

Table 2. Multivariate Analysis of Factors Related to Left Atrial Spontaneous Echo Contrast

	p Value	Odds Ratio (95% CI)
Hematocrit	0.002	2.24 (1.33–3.78)
Fibrinogen	0.008	2.08 (1.21–3.55)
Left atrial dimension	0.004	1.90 (1.23–2.95)
Age	0.03	1.64 (1.05–2.59)
Platelet count	NS	1.44 (0.84–2.46)
White cell count	NS	1.06 (0.62–1.79)
Anticoagulation	NS	0.64 (0.27–1.51)

CI = confidence interval.

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Table 3. Patient Characteristics Related to Recent Embolism

	No Embolism (n = 95)	Embolism (n = 40)	p Value
Left atrial spontaneous echo contrast	39 (41)	35 (87)	< 0.001
Fibrinogen (g/liter)	4.56 ± 1.64	6.00 ± 1.32	< 0.001
White cell count (10^9/liter)	7.03 ± 2.59	8.69 ± 3.61	0.003
Left atrial thrombus	6 (6)	9 (23)	0.006
Age (yr)	64.5 ± 11.3	69.7 ± 9.7	0.01
Anticoagulation	27 (28)	20 (50)	0.02
Platelet count (10^9/liter)	237 ± 81	273 ± 109	0.04
Left atrial dimension (mm)	47.0 ± 7.5	47.9 ± 6.6	NS
Hematocrit (%)	42.5 ± 6.0	41.4 ± 5.8	NS

Values are expressed as number (%) of patient group or mean ± SD.

age, with an extension onto the lateral left atrial wall in one patient. The diameter of the thrombi ranged from 0.7 to 2.6 cm (mean 1.3). Three patients had a mobile thrombus, associated in all with recent embolism and with left atrial spontaneous echo contrast. Compared with patients without left atrial thrombus, patients with left atrial thrombus (n = 15) had a significantly increased prevalence of left atrial spontaneous echo contrast (14 (93%) of 15 patients vs. 60 (50%) of 120 patients, p = 0.001), increased left atrial dimension (50.8 ± 4.7 vs. 46.9 ± 7.4 mm, p = 0.047) and slightly increased fibrinogen concentration (5.43 ± 1.50 vs. 4.93 ± 1.70 g/liter, p = NS). The same factors associated with embolism by univariate and multivariate analyses were also significantly related to the combined end point of embolism and left atrial thrombus (n = 46).

Stable outpatients without previous embolism. Table 4 shows the characteristics of the 40 clinically stable outpatients without previous embolism who underwent additional hematologic studies related to left atrial spontaneous echo contrast. Hematocrit, fibrinogen concentration and left atrial dimension were significantly increased in patients with spontaneous echo contrast. There was no correlation between hematocrit and fibrinogen concentration in these patients (r = 0.11, p = 0.52). In multivariate analysis, left atrial dimension (p = 0.03, odds ratio = 3.59 [95% confidence interval 1.12 to 11.50]), hematocrit (p = 0.02, odds ratio = 3.51 [95% confidence interval 1.19 to 10.30]) and fibrinogen concentration (p = 0.03, odds ratio = 2.70 [95% confidence interval 1.08 to 6.73]) were independently related to left atrial spontaneous echo contrast. Other variables, including platelet count and indexes of platelet activation and turnover, were not significantly related to spontaneous echo contrast. The D-dimer levels remained similar in both groups when the three patients with thrombus (mean D-dimer 106 ng/ml) were excluded.

Discussion

This is the first study to examine the relation between systemic hematologic variables and left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation. Hematocrit and fibrinogen, but not platelet indexes, were

Table 4. Characteristics of 40 Clinically Stable Outpatients Without Previous Embolism Related to Left Atrial Spontaneous Echo Contrast

	Left Atrial Spontaneous Echo Contrast		
	Absent (n = 19)	Present (n = 21)	p Value
Hematocrit (%)	42.2 ± 3.7	45.7 ± 3.6	0.005
Left atrial dimension (mm)	46.0 ± 5.6	50.8 ± 7.5	0.029
Fibrinogen (g/liter)	3.28 ± 0.84	3.93 ± 1.00	0.035
Left atrial thrombus	0 (0)	3 (14)	NS
Age (yr)	62.0 ± 11.8	68.0 ± 8.3	NS
Platelet count (10^9/liter)	221 ± 44	228 ± 66	NS
White cell count (10^9/liter)	6.08 ± 2.03	7.03 ± 1.85	NS
ESR (mm/h)	4.8 ± 4.1	7.8 ± 8.8	NS
Factor VII (%)	97.6 ± 19.4	101.2 ± 19.0	NS
Glycocalicin (ng/ml)	1.92 ± 0.33	1.82 ± 0.53	NS
Glycocalicin index	0.97 ± 0.32	0.83 ± 0.31	NS
Beta-thromboglobulin (ng/ml)	21.4 ± 7.5	21.6 ± 5.6	NS
D-dimer (ng/ml)	101 ± 32	111 ± 54	NS

ESR = erythrocyte sedimentation rate.

independently related to spontaneous echo contrast. These findings are consistent with a role for erythrocytes and fibrinogen in the pathogenesis of left atrial spontaneous echo contrast. The study also confirmed the association between spontaneous echo contrast and thromboembolism in patients with nonvalvular atrial fibrillation, which may be mediated in part by hematologic factors.

Mechanism of spontaneous echo contrast. Sigel et al. (12–14) reported that spontaneous echo contrast in vitro required erythrocytes and fibrinogen and that its intensity correlated with hematocrit and fibrinogen concentration. Erbel et al. (15) reported fibrinogen levels in nine patients with left atrial spontaneous echo contrast associated with mitral valve disease similar to those in the present study (mean 5.2 g/liter). However, hematologic variables were not examined in patients without spontaneous echo contrast (15). The present study shows that hematocrit and fibrinogen concentration are important determinants of left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation. Hematocrit was significantly related to left atrial spontaneous echo contrast in unselected patients only by multivariate analysis, a finding that may reflect the negative correlation between hematocrit and fibrinogen concentration in this patient group. However, hematocrit was significantly related to left atrial spontaneous echo contrast by both univariate and multivariate analysis in clinically stable outpatients.

Sigel et al. (14) also showed that the intensity of spontaneous echo contrast in vitro was inversely related to the blood shear rate, which is the velocity gradient between adjacent fluid layers. Beppu et al. (3) reported that the shear rate of blood in the left atrial cavity was reduced in patients with left atrial spontaneous echo contrast. Left atrial shear rate is proportional to mean left atrial blood velocity divided by left atrial dimension (3). Recent studies (16) have shown that left atrial spontaneous echo contrast is associated with decreased left atrial appendage flow velocities. The relation between left atrial dimension and spontaneous echo contrast in the present study is consistent with an inverse relation between left atrial spontaneous echo contrast and left atrial shear rate.

Hematocrit, fibrinogen concentration and shear rate are also the major determinants of erythrocyte aggregation (17,18). Erythrocyte aggregation reflects a balance between fibrinogen bridging between erythrocytes and electrostatic repulsion by sialic acid residues on the erythrocyte membrane (19,20). The length of the fibrinogen molecule appears to be a key property in its ability to link erythrocytes by keeping adjacent erythrocytes at a distance, thereby diminishing the effect of repulsive forces (20). Increasing shear rate results in progressive disruption of existing aggregates (18).

Sigel et al. (14) concluded that erythrocyte aggregation was the predominant cause of increased echogenicity at low shear rates, with the increased size of erythrocyte aggregates compared with single cells increasing the amplitude of backscattered ultrasound signals. The relation among hematocrit, fibrinogen concentration, left atrial dimension and left atrial spontaneous echo contrast demonstrated in the current study support their hypothesis (14) and suggests that left atrial spontaneous echo contrast is a manifestation of erythrocyte aggregation.

Some investigators have proposed a role for platelet aggregation in the formation of spontaneous echo contrast. Erbel et al. (15) found evidence of increased platelet aggregation in nine patients with left atrial spontaneous echo contrast, and resolution of spontaneous echo contrast with platelet disaggregatory therapy was reported in one patient (21). However, other studies (22,23) have shown no echogenicity with platelet aggregates. Infused platelets may produce large discrete echoes (24) distinct from the smokelike echoes of spontaneous echo contrast. Platelet aggregates do not share the association with stasis that characterizes left atrial spontaneous echo contrast (2,3). In contrast, platelet aggregation may be favored by high shear rate conditions (25). Although platelet count was increased in unselected patients with left atrial spontaneous echo contrast in the present study, this relation was not significant when adjusted for other variables. There was no relation between spontaneous echo contrast and platelet count or indexes of platelet activity in stable outpatients who were receiving aspirin. Nevertheless, the elevated fibrinogen levels associated with left atrial spontaneous echo contrast may also favor platelet aggregation because of interplatelet fibrinogen bridging (26), and it is possible that intermittent platelet aggregation may accompany erythrocyte aggregation and contribute to the association between left atrial spontaneous echo contrast and thromboembolism.

Spontaneous echo contrast and thromboembolism. Daniel et al. (27) reported that left atrial spontaneous echo contrast was an independent marker of left atrial thrombus or previous embolism, or both, in patients with mitral stenosis or a mitral valve prosthesis. We extended this association to patients with nonvalvular atrial fibrillation (2), as confirmed in the present study. Virchow stated that thrombosis resulted from the triad of blood stasis, altered blood characteristics and vessel wall injury. Previous studies (2,3) have shown an association between left atrial spontaneous echo contrast and conditions favoring left atrial stasis, such as atrial fibrillation and mitral stenosis. These conditions are also associated with thromboembolism. We have now shown that left atrial spontaneous echo contrast also reflects altered blood characteristics, therefore indicating a relatively hypercoagulable state in addition to stasis.

Although Sigel et al. (23) found that spontaneous echo contrast preceded thrombosis at low shear rates, the relation between spontaneous echo contrast and in vivo thrombosis is uncertain. Nevertheless, there are several potential mechanisms by which spontaneous echo contrast may represent a prethrombotic state. The present findings support erythrocyte aggregation as the mechanism of spontaneous echo contrast. Erythrocyte aggregation increases blood viscosity

at low shear rates (17), thereby reducing blood flow and increasing the propensity to thrombosis. Intracardiac thrombosis occurs when activation of coagulation factors in low shear rate conditions, rather than activation of platelets, leads to fibrin formation (28). In vitro (22) and in vivo (3) studies suggest that dense spontaneous echo contrast may represent a transition stage in the development of a fibrin-rich red thrombus, with the network of erythrocytes and fibrinogen forming a framework for subsequent thrombus formation. Clinical studies (29,30) have shown increased erythrocyte aggregation in patients with stroke, including cardiogenic stroke, compared with values in control subjects.

Elevated hematocrit and fibrinogen levels associated with left atrial spontaneous echo contrast may favor thrombosis by mechanisms other than erythrocyte aggregation. Both left atrial spontaneous echo contrast and fibrinogen were independently associated with thromboembolism in the present study. This association may reflect independent effects of fibrinogen on thrombosis or acute elevation of fibrinogen concentration after embolic events. Several studies (31,32) have shown that fibrinogen concentration is an independent predictor of cardiovascular disease, including stroke. Fulton and Duckett (33) found a close relation between elevated fibrinogen levels and thromboembolism after myocardial infarction and suggested that fibrinogen may have contributed to the thrombogenic state. Fibrinogen is intimately involved in thrombogenesis (34), with effects on platelet aggregation, as a major determinant of blood viscosity and by effects on atherogenesis. A report from the Framingham study (35) also showed that patients with elevated hematocrit had an increased risk of subsequent stroke.

Previous studies (36) have reported elevated levels of D-dimer, a marker of intravascular coagulation, in patients with nonvalvular atrial fibrillation compared with values in healthy control subjects. Yasaka et al. (37) reported marked elevation of D-dimer in patients with mobile intracardiac thrombi, with no significant difference between patients with nonmobile thrombi and those without thrombi. In the present study, D-dimer levels were not related to the presence of spontaneous echo contrast. Left atrial spontaneous echo contrast in the absence of formed mobile thrombus does not appear to be associated with sufficient solid phase fibrin formation to result in elevated D-dimer levels.

It is an interesting paradox that spontaneous echo contrast and erythrocyte aggregation are not influenced by anticoagulant therapy (12,38), although anticoagulant therapy reduces the incidence of thromboembolism in patients with atrial fibrillation (1). The clotting factors affected by anticoagulant therapy are therefore unlikely to be required for the formation of spontaneous echo contrast. Factor VII levels in the present study were similar in patients with and without left atrial spontaneous echo contrast.

Prognostic value of spontaneous echo contrast. A major potential clinical role of left atrial spontaneous echo contrast is as a predictor of subsequent thromboembolic events, thereby identifying patients likely to benefit most from anticoagulant therapy. The present study indicates that left atrial spontaneous echo contrast reflects hematologic as well as hemodynamic variables. Fibrinogen is an acute phase protein and increases in response to a number of stimuli. Several studies (30,39) have shown acute activation of the coagulation system, including elevated fibrinogen, after stroke. Yasaka et al. (40) reported acute increases in hematocrit at the time of appearance or enlargement of intracardiac thrombus in patients with cardioembolic stroke. Fisher and Meiselman (30) found increased erythrocyte aggregation in patients early after cardiogenic stroke compared with the same patients 2 months later. Hospital inpatients without recent embolism also had a significant increase in fibrinogen concentration and a slight increase in red cell aggregation compared with values in healthy control subjects (30). Tanahashi et al. (29) also demonstrated increased erythrocyte aggregation in patients with acute compared with chronic stroke. Patients with recent embolism in the present study had increased fibrinogen concentration and an increased prevalence of left atrial spontaneous echo contrast.

These results have diverging implications for the prognostic value of left atrial spontaneous echo contrast. The association between hematologic factors and left atrial spontaneous echo contrast suggests additional mechanisms for the association between spontaneous echo contrast and thrombotic events. However, it is likely that left atrial spontaneous echo contrast will be acutely increased after embolic events and may not reflect the baseline state. Long-term follow-up studies of patients with left atrial spontaneous echo contrast will need to consider the clinical status of the patient at the time of initial study, which may influence the hematologic determinants of spontaneous echo contrast.

Limitations of the study. Erythrocyte and platelet aggregation in the left atrium itself were not directly measured in the present study. However, measurement of the systemic determinants of erythrocyte aggregation and platelet indexes were consistent with erythrocyte aggregation as the mechanism of left atrial spontaneous echo contrast. This study included only patients with nonvalvular atrial fibrillation. Hemodynamic factors may be more important in the formation of left atrial spontaneous echo contrast in other patients, such as those with mitral valve disease.

Conclusions. This study has shown that hematocrit, fibrinogen concentration and left atrial dimension are determinants of left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation. Left atrial spontaneous echo contrast therefore reflects a systemic hypercoagulable state, in addition to local left atrial stasis. The study also confirmed the association between left atrial spontaneous echo contrast and thromboembolism. These findings support the hypothesis that left atrial spontaneous echo contrast is due to erythrocyte aggregation in low shear rate conditions and suggest that hematologic factors may contribute to the association between spontaneous echo contrast and throm-

boembolism. Acute variations in hematologic variables, particularly fibrinogen, may affect the presence and intensity of spontaneous echo contrast. Hematologic variables should therefore be measured in studies addressing the prognostic importance of left atrial spontaneous echo contrast.

We thank Barbara Murray for performing laboratory assays and Anthony Freeman, MD for referring patients to the study.

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