

Prognostic Implications of Left Atrial Spontaneous Echo Contrast in Nonvalvular Atrial Fibrillation

DOMINIC Y. C. LEUNG, MBBS, MRCP(UK), FRACP,* IAN W. BLACK, MBBS, FRACP,
GREGORY B. CRANNEY, MBBS, FRACP, ANDREW P. HOPKINS, MBBS, FRACP,
WARREN F. WALSH, MBBS, FRACP, FACC

Sydney, New South Wales, Australia

Objectives. This study examined the influence of left atrial spontaneous echo contrast on the subsequent stroke or embolic event rate and on survival in patients with nonvalvular atrial fibrillation.

Background. Left atrial spontaneous echo contrast is associated with atrial fibrillation and a history of previous stroke or other embolic events. However, the prognostic implications of spontaneous contrast in patients with nonvalvular atrial fibrillation are unknown.

Method. The study group comprised 272 consecutive patients with nonvalvular atrial fibrillation undergoing transesophageal echocardiography. Clinical and echocardiographic data were collected at baseline, and patients were prospectively followed up, and all strokes, other embolic events and deaths were documented. The relation between spontaneous contrast at baseline and subsequent stroke, other embolic events and survival was analyzed.

Results. Left atrial spontaneous echo contrast was detected at baseline in 161 patients (59%). The mean follow-up was 17.5 months. The stroke or other embolic event rate was 12%/year (15 strokes, 3 transient ischemic attacks, 2 peripheral embolisms) in

patients with, compared with 3%/year (5 strokes) in patients without, baseline spontaneous contrast ($p = 0.002$). In 149 patients without previous thromboembolism, the event rate was 9.5%/year in patients with and 2.2%/year in patients without spontaneous contrast ($p = 0.003$). There were 25 deaths in patients with and 11 deaths in patients without spontaneous contrast. Patients with spontaneous contrast had significantly reduced survival ($p = 0.025$). On multivariate analysis, spontaneous contrast was the only positive predictor (odds ratio 3.5, $p = 0.03$) and warfarin therapy on follow-up the only negative predictor (odds ratio 0.23, $p = 0.02$) of subsequent stroke or other embolic events.

Conclusions. Transesophageal echocardiography can risk-stratify patients with nonvalvular atrial fibrillation by identifying left atrial spontaneous echo contrast. These patients have both a significantly higher risk of developing stroke or other embolic events and a reduced survival, and they may represent a subgroup in whom the risk/benefit ratio of anticoagulation may be most favorable.

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Left atrial spontaneous echo contrast refers to swirling smoke-like echoes that are detected by transesophageal echocardiography in conditions favoring stasis of blood in the left atrium. We previously showed (1) that left atrial spontaneous echo contrast is significantly associated with the presence of atrial fibrillation, mitral stenosis, left atrial enlargement and left atrial thrombus. Left atrial spontaneous echo contrast has also been shown to be associated with a history of thromboembolism, both in patients with mitral stenosis or prosthetic mitral valves (1,2) and in those with nonvalvular atrial fibrillation (1). However, the prognostic implications of left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation are unknown. The aim of the present study was to determine

prospectively the influence of left atrial spontaneous echo contrast on both the subsequent development of stroke or other embolic events and survival in a large series of patients with nonvalvular atrial fibrillation.

Methods

Study patients. The study patients comprised 272 consecutive patients with nonvalvular atrial fibrillation undergoing transesophageal echocardiography at our institution between January 1989 and January 1993. Criteria for inclusion were atrial fibrillation with a duration >7 days, with no evidence of rheumatic mitral stenosis, moderate or severe mitral regurgitation and no history of mitral valve surgery. All clinical characteristics, including patient gender and age, details of previous stroke or embolic events and study indication, were recorded at baseline. There were 185 men and 87 women with a mean (\pm SD) age of 68 ± 11 years (range 24 to 87). The indications for transesophageal echocardiographic studies were exclusion of left atrial thrombus in patients without previous thromboembolism

From the Department of Cardiovascular Medicine, Prince Henry Hospital, Sydney, New South Wales, Australia.

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*Present address and address for correspondence: Dr. Dominic Leung, Department of Cardiology, The Cleveland Clinic Foundation, Desk F15, Cleveland, Ohio 44195.

(n = 129, 47%), suspected cardiac source of embolism (n = 106, 39%), suspected infective endocarditis (n = 11, 4%), assessment of mitral regurgitation (n = 5, 2%), aortic valve disease (n = 6, 2%) and miscellaneous findings (n = 15, 6%).

Echocardiographic studies. All patients underwent both transthoracic and transesophageal echocardiographic studies, with all echocardiographic data recorded prospectively at baseline. Transthoracic studies were performed using 2.5- and 3.5-MHz phased array transducers with a Hewlett-Packard Sonos 1000 system using all standard echocardiographic windows. Global left ventricular systolic function was assessed semiquantitatively from the parasternal and apical views and graded as normal or mild, moderate or severe impairment. Left atrial dimension and left ventricular wall thickness were measured according to standard M-mode criteria (3). Only moderate or severe left ventricular hypertrophy (wall thickness ≥ 13 mm) was considered significant. Mitral annular calcification was diagnosed on M-mode and two-dimensional echocardiography by the presence of an echo-dense band posterior to the posterior mitral leaflet at the atrioventricular junction with motion parallel to that of the free left ventricular wall (4). Mitral regurgitation was assessed semiquantitatively by color and continuous wave Doppler and was graded as trivial or mild, moderate or severe (5).

Transesophageal echocardiography was performed using 5-MHz phased array transducer(s) according to standard protocols (6). Written informed consent was obtained in all patients. Biplane examination was performed in 145 patients, monoplane in 115 and multiplane in 12. No complications were recorded. Only the first study was analyzed if patients had subsequent studies.

Left atrial spontaneous echo contrast and left atrial thrombus, if present, were specifically examined. Left atrial spontaneous echo contrast was diagnosed by the presence of characteristic dynamic smoke-like swirling echoes in the left atrium or the atrial appendage, distinct from background white noise caused by excessive gain (7). The presence or absence of left atrial spontaneous echo contrast was determined by two independent experienced observers, and any discrepancy was resolved by consensus. Left atrial thrombus was diagnosed by the presence of an echo-dense mass in the left atrium or the left atrial appendage distinct from the endocardium and the pectinate muscles of the left atrial appendage (8). The presence of atheroma in the thoracic aorta was examined and classified as simple or complex according to previously defined criteria (9).

Follow-up. Patients were prospectively followed up to determine the incidence of subsequent stroke or other embolic events. Follow-up information was obtained by telephone interviews, careful review of hospital records and direct contact with the patients' primary physicians. Patients' medication history, including warfarin and aspirin therapy at the time of follow-up, was recorded. The primary end point was stroke or other embolic events. Stroke was defined as a definite focal neurologic deficit of acute onset consistent with a vascular event lasting >24 h. A transient ischemic attack was defined as

Table 1. Baseline Clinical and Echocardiographic Findings Related to Left Atrial Spontaneous Echo Contrast

| | SEC Present (n = 161) | SEC Absent (n = 111) | p Value |
|-----------------------------------|--------------------------|-------------------------|---------|
| Previous thromboembolism | 86 (53%) | 26 (23%) | < 0.001 |
| Left atrial thrombus | 19 (12%) | 0 | < 0.001 |
| Age (yr) | 70 \pm 9 | 65 \pm 12 | < 0.001 |
| Left atrial dimension (mm) | 50 \pm 7 | 45 \pm 7 | < 0.001 |
| Complex aortic atheroma | 23 (14%) | 5 (4.5%) | 0.009 |
| Mitral annular calcification | 57 (35%) | 27 (24%) | 0.06 |
| Male patients | 103 (64%) | 58 (52%) | 0.085 |
| Moderate or severe LV dysfunction | 28 (17%) | 14 (13%) | 0.284 |
| Significant LV hypertrophy | 18 (11%) | 11 (10%) | 0.739 |

Data presented are mean value \pm 1 SD or number (%) of patients. LV = left ventricular; SEC = spontaneous echo contrast.

focal neurologic deficit of sudden onset that resolved completely in <24 h. Transient ischemic attack was considered an embolic event. The criteria for embolism to viscera or to an extremity were pain and other symptoms and signs consistent with abrupt vascular occlusion. The results of investigations performed after the suspected thromboembolic event were also recorded. The secondary end point was all-cause mortality. Sudden death was not considered an embolic event. All end point events were assessed by a worker unaware of the results of the echocardiographic studies.

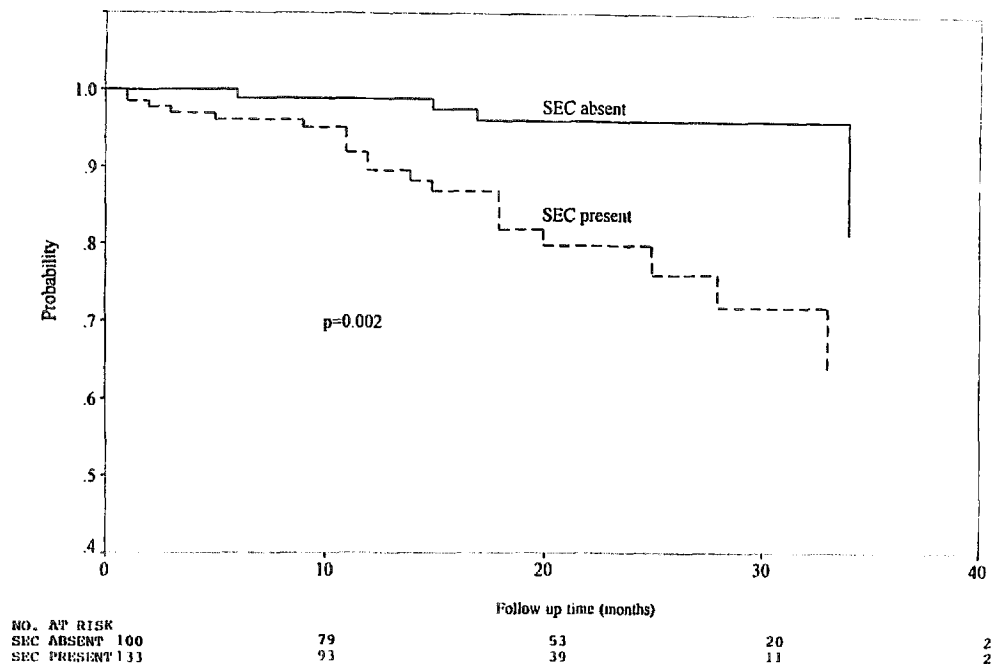
Statistical analysis. Results are reported as mean value \pm 1 SD, unless otherwise stated. Unpaired Student *t* test was used to compare continuous variables, and chi-square test to compare categorical variables. Multivariate logistic regression analysis (maximal likelihood ratio method) was used to identify independent predictors of subsequent thromboembolic events. Actuarial survival and freedom from stroke or other embolic events were plotted by the Kaplan-Meier method, and subgroups were compared by the log-rank test. Odds ratios were shown with 95% confidence intervals, and statistical significance was defined as a two-tailed p value <0.05 . The statistical package SPIDA (version 6) was used for statistical analysis.

Results

Baseline clinical and echocardiographic findings. Left atrial spontaneous echo contrast was detected by transesophageal echocardiography in 161 (59%) of the 272 patients. Forty-two patients (15%) had moderate or severe left ventricular systolic dysfunction, and 29 (11%) had significant left ventricular hypertrophy. Mitral annular calcification was detected in 84 patients (31%). Ninety-six patients (35%) had simple thoracic aortic atheroma, and 28 (10%) had complex atheroma. Eighty-eight patients (32%) had a history of stroke or transient ischemic attack, and 24 (9%) had a history of an embolic event affecting either an extremity or a visceral organ.

The clinical and echocardiographic findings of patients with (group A) and without (group B) baseline left atrial spontaneous echo contrast are compared in Table 1. Patients in group

Figure 1. Cumulative freedom from stroke or other embolic events in patients with (SEC present) and without (SEC absent) baseline left atrial spontaneous echo contrast (SEC).



A were significantly older ($p < 0.001$), had a higher incidence of previous thromboembolic events ($p < 0.001$), larger left atrial dimension ($p < 0.001$) and higher prevalence of complex thoracic aortic atheroma ($p = 0.009$). The prevalence of mitral annular calcification, moderate or severe left ventricular systolic dysfunction or significant left ventricular hypertrophy were not different between the two groups.

Nineteen patients (7%) were found to have a left atrial thrombus, and three had a left ventricular apical thrombus. The left atrial thrombus was situated in the atrial appendage in 16 patients and at the orifice of the appendage in 3. All 19 patients with left atrial thrombus had left atrial spontaneous echo contrast. These 22 patients were excluded from all subsequent analysis.

Follow-up. Follow-up was complete in 233 patients (93%), with a mean duration of follow-up of 17.5 ± 10 months (maximal follow-up 47 months). Seventeen patients (7%) were lost to follow-up. Forty-five patients (34%) in group A and 11 (11%) in group B were receiving anticoagulation therapy with warfarin on follow-up ($p < 0.001$), whereas 42 patients (32%) in group A and 47 (47%) in group B were receiving aspirin therapy ($p = 0.02$).

Twenty-five patients had a stroke or other embolic event during follow-up (overall event rate 7%/year). The total event rate was 12%/year in group A and 3%/year in group B, and the event rate for stroke or transient ischemic attack only was 10.5%/year in group A and 3%/year in group B. Patients in group A had a significantly decreased freedom from stroke or other embolic event compared with those in group B ($p = 0.002$) (Fig. 1).

In group A, 15 patients had a stroke, two fatal. Fourteen patients had a cerebral computed tomographic scan performed after the event; these showed nonhemorrhagic cerebral infar-

tion in 13 patients and no significant abnormality in 1. The one patient who did not have a computed tomographic scan died within 24 h of the onset of neurologic deficit, and autopsy was not performed. Three patients had transient ischemic attacks. A computed tomographic scan was performed in one of these three patients and showed no significant abnormalities. One patient had an acute embolism to the right brachial artery, and another had an acute embolism to the left femoral artery. These two patients underwent surgical embolectomy, which confirmed the diagnosis. In the 45 patients in group A receiving warfarin therapy, the incidence of stroke or other embolic events was 7%/year compared with 14.5%/year in the 88 patients not receiving warfarin therapy ($p = 0.15$). Thirty of these 45 patients (67%) receiving warfarin therapy had a previous embolism, whereas only 34 patients (39%) of the 88 patients not receiving warfarin had such a history ($p = 0.002$).

In group B, five patients had a stroke on follow-up, two fatal. Three patients had a computed tomographic scan performed; these showed nonhemorrhagic cerebral infarction in one patient and no significant abnormalities in two. One of the latter two patients had a brainstem event that was confirmed by magnetic resonance imaging. The two patients who died did not have a computed tomographic scan performed. No patient in group B had a peripheral embolism or transient ischemic attack on follow-up.

There were a total of 36 deaths on follow-up (overall all-cause mortality 10.5%/year). According to life-table analysis, patients in group A had a significantly reduced survival compared with those in group B ($p = 0.025$) (Fig. 2). In group A, there were 25 deaths. Nine patients died of cardiovascular causes, two died of fatal stroke, six died of complications secondary to a stroke or peripheral embolism, four died of cancer and four of other noncardiovascular causes. In group B,

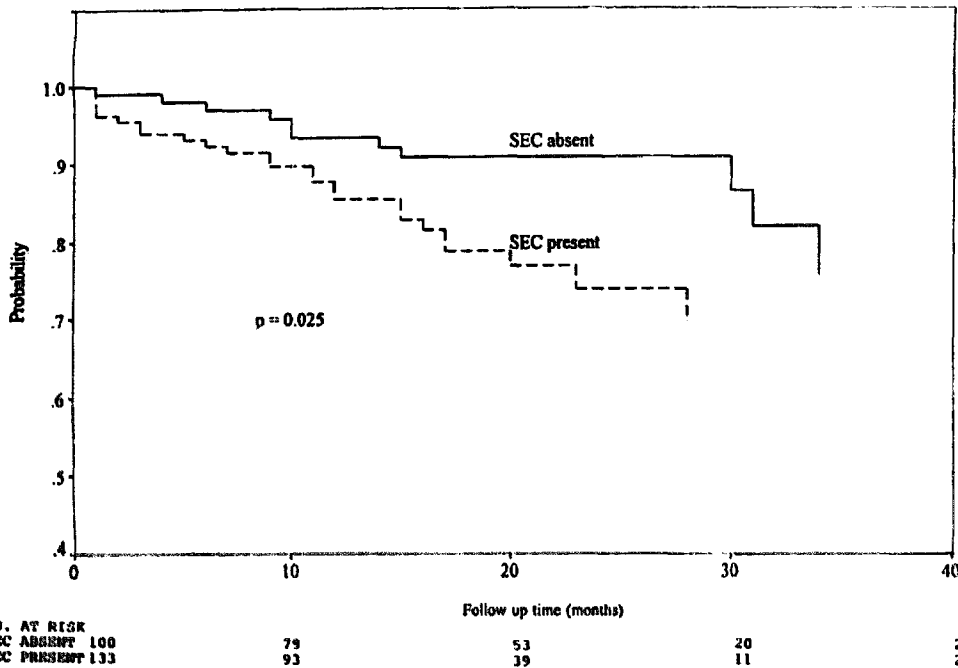


Figure 2. Survival curves of patients with (SEC present) and without (SEC absent) baseline left atrial spontaneous echo contrast (SEC).

there were 11 deaths. Four patients died of cardiovascular causes, two died of fatal stroke, three died of cancer and two of other causes.

Patients without a history of stroke or embolic events. One hundred forty-nine patients did not have history of previous stroke or other embolic events. Left atrial spontaneous echo contrast was detected in 69 of these patients (46%). In these 149 patients, the event rate for stroke or other embolic events was 9.5%/year in patients with baseline left atrial spontaneous

echo contrast and 2.2%/year in patients without. In the patients with spontaneous echo contrast, seven had a stroke, and one patient had an acute embolism to the left femoral artery. In the patients without spontaneous echo contrast, three had a stroke. In these patients with no history of previous thromboembolism, patients with left atrial spontaneous echo contrast had significantly decreased freedom from stroke or other embolic events ($p = 0.003$) (Fig. 3). There were 18 deaths on follow-up, 12 in the group with spontaneous echo contrast and

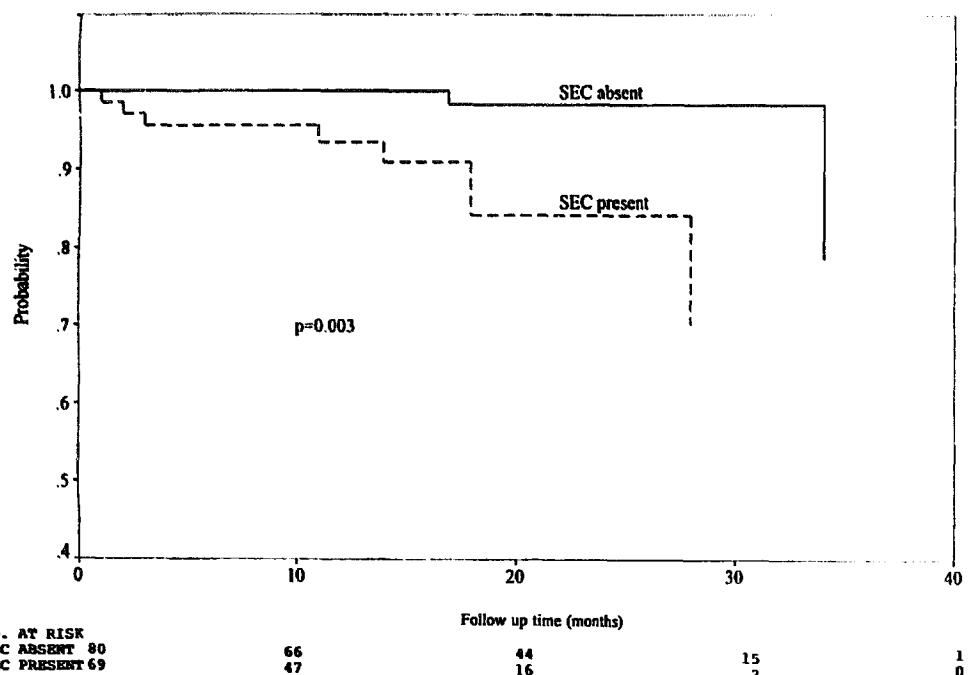


Figure 3. Cumulative freedom from stroke or other embolic events in the 149 patients without a history of thromboembolism. SEC = left atrial spontaneous echo contrast.

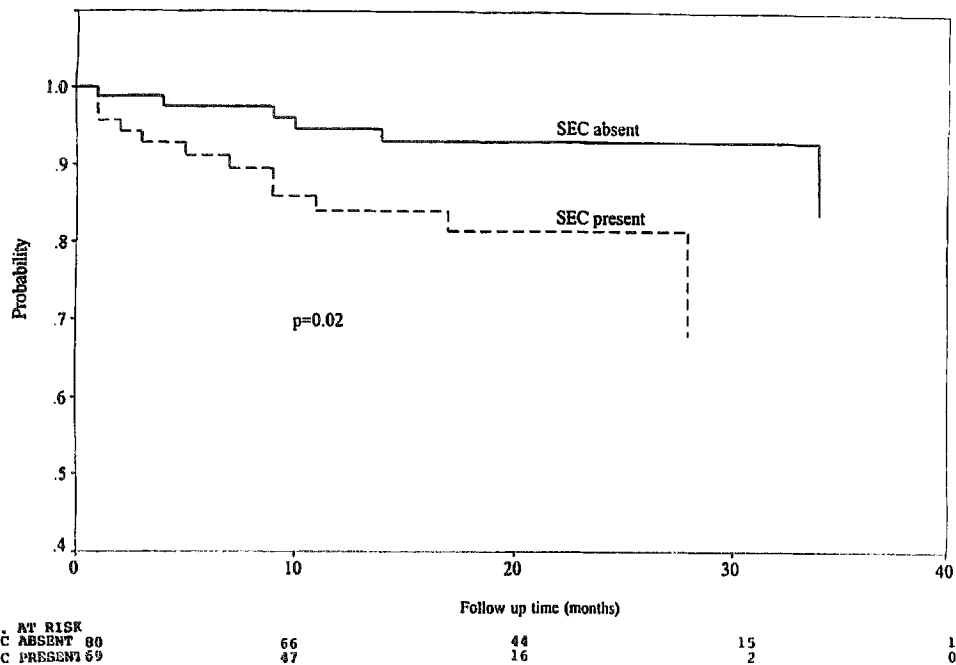


Figure 4. Survival curves of 149 patients without a history of thromboembolism. SEC = left atrial spontaneous echo contrast.

6 in the group without. On life-table analysis, patients with left atrial spontaneous echo contrast had significantly reduced survival ($p = 0.02$) (Fig. 4).

Predictors of subsequent stroke or other embolic events. Table 2 shows the results of multivariate logistic regression analysis performed to identify independent predictors of subsequent stroke or other embolic events in this cohort of 233 patients on the basis of clinical characteristics, baseline echocardiographic variables and warfarin or aspirin therapy on follow-up. The presence of left atrial spontaneous echo contrast at baseline was the only independent positive predictor, and anticoagulation therapy with warfarin on follow-up the only independent negative predictor, of subsequent stroke or other embolic events. Gender, age, previous thromboembolism, moderate or severe left ventricular systolic dysfunction,

significant left ventricular hypertrophy, left atrial dimension, left atrial spontaneous echo contrast, mitral annular calcification, complex thoracic aortic atheroma and warfarin or aspirin therapy on follow-up were used as covariates.

Complex thoracic aortic atheroma was not a significant predictor on either univariate ($p = 0.5$) or multivariate analysis. The results of the multivariate analysis were not altered after patients with complex atheroma were excluded from the analysis, with spontaneous echo contrast being an independent positive predictor ($p = 0.04$, odds ratio 3.3, 95% confidence interval [CI] 1.1 to 10.2) and warfarin therapy on follow up a negative predictor ($p = 0.02$, odds ratio 0.2, 95% CI 0.05 to 0.75).

Discussion

This large prospective study is the first to examine the prognostic implications of left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation. We showed that patients with left atrial spontaneous echo contrast have on follow-up both a higher risk of developing stroke or other embolic events and a reduced actuarial survival. Moreover, the presence of left atrial spontaneous echo contrast was the only independent positive predictor of subsequent thromboembolic events, including stroke, transient ischemic attack and peripheral embolism.

Prevalence of left atrial spontaneous echo contrast. Left atrial spontaneous contrast was detected in 59% of the patients. The reported prevalence of left atrial spontaneous echo contrast ranges from 16% to 19% (1,10) in all patients undergoing transesophageal echocardiography and is higher in patients with mitral stenosis or a mitral prosthesis (25% to 74%) (1,2,10). Left atrial spontaneous echo contrast has been shown to be

Table 2. Multivariate Analysis of Clinical and Echocardiographic Factors Related to Subsequent Thromboembolism in 233 Patients With Nonvalvular Atrial Fibrillation

| | p Value | Odds Ratio | 95% CI |
|-----------------------------------|---------|------------|----------|
| Spontaneous echo contrast | 0.03 | 3.5 | 1.1-10.5 |
| Warfarin therapy on follow-up | 0.02 | 0.23 | 0.07-0.8 |
| Previous thromboembolism | 0.11 | 2 | 0.8-5.6 |
| Moderate or severe LV dysfunction | 0.17 | 2.3 | 0.7-7.3 |
| Aspirin therapy | 0.19 | 0.5 | 0.2-1.4 |
| Significant LV hypertrophy | 0.37 | 0.4 | 0.05-3.1 |
| Female gender | 0.38 | 1.6 | 0.6-4.2 |
| Mitral annular calcification | 0.58 | 1.3 | 0.5-3.4 |
| Left atrial dimension | 0.63 | 1 | 0.9-1 |
| Age | 0.89 | 1 | 0.9-1 |
| Complex aortic atheroma | 0.98 | 1 | 0.2-4.3 |

CI = confidence interval; LV = left ventricular.

strongly associated with the presence of atrial fibrillation (1), but previous reports of its prevalence in nonvalvular atrial fibrillation are sparse. Our group reported a prevalence of 47% in a smaller series of patients (1), and Tsai et al. (11) reported a prevalence of 24% in a series of 103 patients.

Thromboembolic risk in nonvalvular atrial fibrillation.

There is a definite increase in the risk of stroke or other embolic events in patients with nonvalvular atrial fibrillation (12,13). The reported incidence of stroke or other embolic events in these patients ranges from 3%/year to 7.4%/year (14-18). In the placebo arm of the Stroke Prevention in Atrial Fibrillation study (15), the event rate for stroke, transient ischemic attack or systemic embolism was 9%/year. The present study confirmed the significantly increased risk of thromboembolism in these patients, with an event rate of 5.8%/year for stroke, 6.7%/year for stroke or transient ischemic attack, and 7%/year for all thromboembolic events.

The risk of subsequent stroke and other embolic events is clearly not uniform among patients with nonvalvular atrial fibrillation (13). There has been considerable interest in identifying clinical risk factors for thromboembolism in these patients. Female gender (19), older age group (20), hypertension (15,20,21), recent congestive heart failure (22) and a history of thromboembolism (20,22) have been reported to be useful clinical predictors in some studies. Analysis of the result of the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (AFASAK) study (23) for risk factors showed that only a history of previous myocardial infarction was a useful predictor of thromboembolism.

The search for echocardiographic predictors of thromboembolism has also yielded conflicting results. Although left atrial enlargement is the most frequently reported predictor (19,21,24-26), left ventricular dysfunction (24), left ventricular hypertrophy (25) and mitral annular calcification (15,18) have been shown to be significant in some studies. However, these echocardiographic variables have not been predictive in other series (23,27). Many of these studies were limited by being retrospective in design (11,20,21,26,27), and factors associated with a history of thromboembolism may not necessarily be risk factors for subsequent events.

With the exception of the detection of left atrial thrombus, transesophageal echocardiography has not been previously used to risk-stratify patients with nonvalvular atrial fibrillation. Presence of left atrial thrombus, now reliably detectable by transesophageal echocardiography (28), may define a subgroup of patients at higher risk of thromboembolic events who require anticoagulation. However, a left atrial thrombus was detected in only 19 (7%) of our 272 patients and in 9 (6%) of 150 patients in the Castello et al. (10) study and therefore may have limited applicability.

We previously showed (1) that left atrial spontaneous echo contrast and left atrial thrombus are strongly linked and are associated with a history of thromboembolic events. Therefore, we postulated that the presence of spontaneous echo contrast may also be predictive of subsequent thromboembolic events. The present study showed that left atrial spontaneous echo

contrast is the only significant independent predictor of the increased risk of subsequent stroke or other embolic events. Because the total patient group included a number of patients with a history of previous thromboembolism with a higher prevalence of spontaneous echo contrast who might be expected to have a higher risk of recurrent stroke or other embolic events, we also analyzed the patient subgroup who did not have a history of previous thromboembolism. Life-table analysis demonstrated that these latter patients with spontaneous echo contrast also have both significantly decreased freedom from stroke or other embolic events and reduced survival compared with those without spontaneous echo contrast.

Left atrial enlargement and older age group, although more prevalent in patients with left atrial spontaneous echo contrast, were not significant predictors in the present study. Complex thoracic aortic atheroma has been suggested as a useful predictor of embolic events in recent studies (9,29), but it was not predictive of embolism in the present study, even on univariate analysis. However, the number of patients with this abnormality was small in this series.

Left atrial spontaneous echo contrast and thromboembolism. The strong predictive value of left atrial spontaneous echo contrast raises the question of the possible mechanism linking spontaneous echo contrast with thromboembolism. In an earlier study, our group showed that left atrial spontaneous echo contrast was independently related to hematocrit and fibrinogen concentration (30) and may represent a hypercoagulable state resulting from the interaction between hemologic factors favoring erythrocyte aggregation and hemodynamic factors favoring stasis. Platelet aggregation has also been implicated in the formation of spontaneous echo contrast (31,32). We therefore postulate that spontaneous echo contrast may be a precursor of thrombus formation, especially in foci of low blood flow such as the appendage. These thrombi may then subsequently embolize to major organs.

The present study also showed that left atrial spontaneous echo contrast is associated with more advanced atherosclerotic disease in the thoracic aorta, which suggests that these patients may also have more extensive atherosclerotic disease elsewhere in the aorta and in the cerebral vessels. Systemic embolization, such as was responsible for stroke in these patients with atrial fibrillation, may arise from abnormal segments in these vessels and not necessarily from the heart.

Left atrial spontaneous echo contrast and mortality. The all-cause mortality rate of patients in atrial fibrillation is about twice that of patients in sinus rhythm (13,33,34). This study is the first to show that the mortality risk of patients with nonvalvular atrial fibrillation can be further stratified according to the presence or absence of left atrial spontaneous echo contrast. The reduced survival of patients with spontaneous echo contrast is most probably related to the excess thromboembolic risk and associated vascular disease. Furthermore, patients with spontaneous echo contrast were older, had a higher prevalence of complex aortic atheroma and had a more frequent history of previous thromboembolism consistent with more extensive atherosclerotic vascular disease.

Role of anticoagulant therapy. Recent placebo-controlled studies have shown that anticoagulation with warfarin decreases the thromboembolic risk in patients with nonvalvular atrial fibrillation, but the role of aspirin remains uncertain (14-18). In the present study, warfarin therapy was a significant negative predictor of subsequent stroke or other embolic events on multivariate analysis. In patients with baseline spontaneous echo contrast, the incidence of stroke or other embolic events in those receiving warfarin therapy was 7%/year in contrast to 14.5%/year in those not receiving warfarin therapy. Although it did not reach statistical significance on univariate analysis, this trend toward risk reduction with warfarin therapy occurred despite a higher incidence of previous embolism in the former group of patients. Moreover, patients receiving warfarin therapy were a highly selected subgroup in whom the risk of developing an event was considered high. However, these findings must be interpreted with caution because the study was only observational and did not control for anticoagulation therapy. Nevertheless, these results are consistent with the findings of randomized multicenter trials (14-18).

Study limitations. This was an observational study in a cohort of patients where the presence or absence of spontaneous echo contrast and anticoagulation therapy were not controlled, and there were differences in the baseline characteristics of the two patient subgroups. Nevertheless, spontaneous echo contrast was present in ~50% of the patients at the baseline study, and multivariate analysis was used to allow for these differences in the clinical characteristics of the two patient subgroups. The adverse prognostic implications of the presence of spontaneous echo contrast were highly significant and were independent of history of previous thromboembolism.

No information was available about the natural history of spontaneous echo contrast because serial transesophageal studies were not routinely performed on follow-up or at the time of a thromboembolic event. More information is required to characterize more precisely any changes in spontaneous echo contrast with time or with subsequent thromboembolic events.

Clinical implications. Patients with nonvalvular atrial fibrillation have about a fivefold increase in stroke rate compared with patients in sinus rhythm (13). Anticoagulation therapy with warfarin in patients with nonvalvular atrial fibrillation has been shown to reduce this thromboembolic event rate (14-18). However, warfarin therapy for patients with nonvalvular atrial fibrillation is not uniformly prescribed because of concern about bleeding risk in this predominantly elderly patient population. This is illustrated by the finding that only 24% of patients in the present study were receiving warfarin therapy on follow-up. In the Stroke Prevention in Atrial Fibrillation Study (15), 53% of the study patients were considered ineligible for anticoagulation. In the Stroke Prevention in Nonrheumatic Atrial Fibrillation trial (32), 40% of the patients screened were considered to have contraindications to anticoagulation. Despite careful screening, warfarin

therapy is associated with a significant increase in the risk of bleeding (14-18) in patients with nonvalvular atrial fibrillation. In large, carefully controlled randomized trials, the reported incidence of intracranial hemorrhage and major bleeding on warfarin therapy was up to 2.5%/year (16). The risk/benefit ratio of systemic anticoagulation can be optimized by treating patients at higher risk of developing subsequent thromboembolism. We have shown that transesophageal echocardiography can be used to risk-stratify patients with nonvalvular atrial fibrillation by identifying patients with left atrial spontaneous echo contrast who have both a significantly higher risk of developing stroke, transient ischemic attack or other embolic events and reduced survival. These patients may represent a subgroup in whom the risk/benefit ratio of long-term anticoagulation with warfarin therapy appears most favorable. These findings need to be tested in prospective, randomized, multicenter trials.

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