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Patients With Atrial Fibrillation and Dense Spontaneous Echo Contrast at High Risk

A Prospective and Serial Follow-Up Over 12 Months With Transesophageal Echocardiography and Cerebral Magnetic Resonance Imaging

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OBJECTIVES We sought to assess the prognosis of patients with atrial fibrillation (AF) and dense spontaneous echo contrast (SEC) and to determine the incidence of cerebral embolism under continued oral anticoagulation.

BACKGROUND Patients with AF and dense SEC have an increased risk of cerebral embolism. However, there is little knowledge about the long-term fate and the rate of clinical silent cerebral embolism under continued oral anticoagulation.

METHODS Between 1998 and 2001, all consecutive patients with AF and dense SEC were included in the study. We performed serial and prospective transesophageal echocardiography, cranial magnetic resonance imaging, and clinical examinations during a period of 12 months.

RESULTS A total of 128 patients with dense SEC and AF were included. The control group consisted of 143 patients with faint SEC and AF. During the follow-up period, three patients (2%) had cerebral embolism with neurologic deficits. A total of eight patients (6%) died due to embolic events, and 19 (15%) patients had silent embolism, as documented on cerebral magnetic resonance imaging. Patients with an event had significantly lower left atrial appendage peak emptying velocities and more commonly had a history of previous thromboembolism and denser SEC, as compared with patients without an event.

CONCLUSIONS Patients with AF and dense SEC have a high likelihood of cerebral embolism (22%) and/or death, despite oral anticoagulation. Low peak emptying velocities of the left atrial appendage and dense SEC are independent predictors of an event. (J Am Coll Cardiol 2005;45: 1807–12) © 2005 by the American College of Cardiology Foundation

Dense spontaneous echo contrast (SEC) is found in 12% to 67% of patients with atrial fibrillation (AF), depending on the patient population (1–5). Patients with AF and SEC have an increased risk of cerebral embolism (1,4,6).

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However, there is little knowledge about the long-term fate of patients with permanent AF and SEC, as well as the incidence of cerebral embolism in those patients. Cranial magnetic resonance imaging (MRI) has a high accuracy for detecting cerebral embolism. Furthermore, modern cranial MRI allows the detection of cerebral microembolism (7–10). Therefore, we chose to monitor patients with dense SEC by means of cerebral MRI during the follow-up period.

The aims of this study were: 1) to assess the long-term fate of patients with dense SEC under continued oral anticoagulation; 2) to evaluate the incidence of cerebral embolism during a follow-up period of 12 months; and 3) to determine the predictors of cerebral embolism.

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METHODS

Study patients. Between 1998 and 2001, all patients >18 years of age with permanent nonvalvular AF and SEC were included in the study. Exclusion criteria were contraindication to cerebral MRI, transesophageal echocardiography (TEE), and oral anticoagulation; carotid artery stenosis >50%; valvular heart disease; and the inability to give written, informed consent. Written, informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of the University of Bonn.

Study protocol. Patients were subclassified into two groups: patients with dense SEC (study patients) and patients with faint SEC (control subjects). After all patients were examined clinically, we performed assessment of the cardiovascular risk factors (arterial hypertension, smoking, diabetes mellitus, dyslipoproteinemia, and a history of previous embolism). A 12-lead surface electrocardiogram was obtained. The follow-up time was presumed to be 12 months.

Echocardiographic studies. All studies were conducted with commercially available equipment (System V or Vivid

Abbreviations and Acronyms

AF = atrial fibrillation
INR = international normalized ratio
LA = left atrium/atrial
LAA = left atrial appendage
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MRI = magnetic resonance imaging
SEC = spontaneous echo contrast
TEE = transesophageal echocardiography

V, GE, Milwaukee, Wisconsin). For TEE, a 1.7/3.4-MHz electronic transducer was used. The M-mode left atrial (LA) dimension and left ventricular ejection fraction (LVEF) were measured according to the recommendations of the American Society of Echocardiography (11).

Transesophageal echocardiography was performed with a 6.7-MHz multiplane electronic transducer, as previously reported by our study group (12,13). Cine loops of the LA and left atrial appendage (LAA) were stored. The sample volume of the pulsed Doppler was placed 1 cm into the orifice of the LAA, and the profile of the velocities was recorded.

Echocardiographic data analysis. Echocardiographic evaluations were performed by two independent observers examining the digitized images after the original examination. The images were displayed in random order without clinical information on the patient and analyzed by means of the evaluation software provided by the manufacturer (Echopac, GE). Interobserver differences were resolved by a third observer.

The cine loops of the LA and LAA were examined for thrombi and SEC. The degree of SEC was categorized as being either absent (0), mild (1+), mild to moderate (2+), moderate (3+), or severe (4+), on the basis of the system described by Fatkin et al. (14) (Fig. 1). The LAA area and peak emptying velocities were measured as previously reported (15).

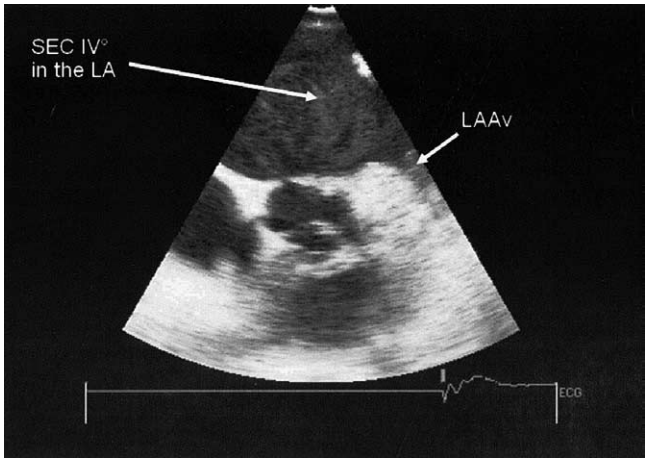

Figure 1. Transesophageal echocardiography with dense spontaneous echo contrast (SEC). LA = left atrium; LAAv = left atrial appendage peak emptying velocity.

Anticoagulation. Patients without effective anticoagulation at admission received intravenous weight-adjusted unfractionated heparin (17 U/kg/h) during hospitalization; further dose adjustments were performed to achieve an activated partial thromboplastin time ratio of 1.5 to 2.5 times of the control value, which was presumed to be effective. Before discharge, all patients were transferred to oral anticoagulation with phenprocoumon. The effectiveness of anticoagulation was assessed by the international normalized ratio (INR) level. An INR >2.0 was defined as a therapeutic range. The target INR was 2.5.

Cranial MRI. Magnetic resonance imaging was done at a 12-month follow-up from the admission and after 1, 3, 6, and 12 months. The MRI examinations were performed with a 1.5-T system (Gyroscan ACS-NT, Philips Medical Systems, Eindhoven, the Netherlands). The imaging protocol included a diffusion-weighted, single-shot, spin echo echoplanar sequence (diffusion gradient b values of 0, 500, and 1,000 s/mm^2, repetition time [TR] of 4,000 ms, echo time [TE/TEd] of 120 ms/85 ms, slice thickness of 6 mm, and matrix 101 × 256), turbo fluid-attenuated inversion recovery (FLAIR) (TR/TE 6,000/100 ms), and T2-weighted turbo spin echo (TR/TE 3,700/90 ms) sequences. The acquisition time for the diffusion-weighted sequences was 36 s (Fig. 2).

Diffusion-weighted images were acquired with diffusion gradients applied in three orthogonal directions. All MRI studies were evaluated by experienced consultant radiologists blinded to the neurologic status and procedure.

The MRI scans of the brain were evaluated for the presence of focal diffusion abnormalities (bright lesions in the diffusion-weighted image) in a pattern consistent with embolic lesions (i.e., cortical or subcortical localization or in the vascular territory of perforating arteries). Diffuse alterations in the diffusion-weighted sequence or a pattern of watershed ischemia were not considered to be embolic types of lesions. Number, size (<5, 5 to 10, or >10 mm), and vascular territory of all focal diffusion abnormalities were recorded.

In patients who showed a focal diffusion abnormality, a follow-up MRI, including T2-weighted, turbo spin echo, and fluid-attenuated inversion recovery sequences was performed after three months to define the presence or absence of a subsequent infarct at the location of the diffusion abnormality.

Neurologic examination. Patients underwent neurologic assessments during a 12-month follow-up period at admission and after 1, 3, 6, and 12 months. The assessments were done by a Board-certified neurologist. A neurologic complication was defined as any new cranial nerve, motor, or sensory deficiency, reflex change, pyramidal sign, or occurrence of mental alteration.

Ultrasound of the cerebral arteries. All patients underwent ultrasound examination (HDI 3000, ATL, Bothell,

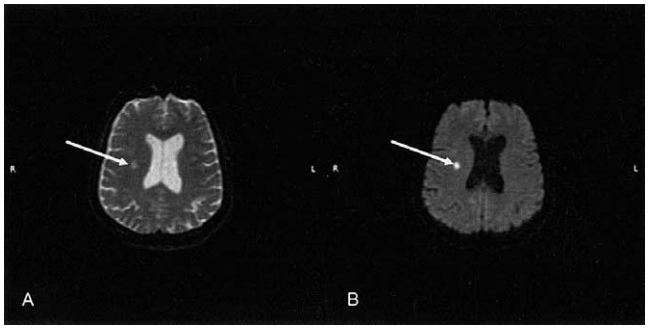

Figure 2. Cerebral magnetic resonance imaging scan in **(A)** T2- and **(B)** diffusion-weighted imaging with **(arrow)** a cerebral lesion after an embolic event.

Washington) at admission and after 1, 3, 6, and 12 months for detection of atherosclerotic lesions of the carotid arteries. Considering all information from B-mode, color Doppler, and Doppler ultrasound, stenoses of the common or internal carotid artery were measured as a reduction of the luminal area, according to established criteria. All patients with stenoses >50% were excluded from the study.

Statistical analysis. Data are reported as the mean value ± SD. Continuous variables between groups were compared by a *t* test for unpaired observations. Nominal data were compared by the Fisher exact test. Categorial data (degree of SEC) were compared by the Wilcoxon signed rank test for matched pairs. In all cases, a p value <0.05 was considered statistically significant. The 95% confidence intervals are given.

RESULTS

Patients. A total of 293 patients with SEC and permanent AF were screened for enrollment in the study. Twenty-two patients were excluded due to pacemaker insertion and/or inability to keep follow-up visits. The study group consisted of 128 patients with dense SEC, and 143 patients with faint SEC comprised the control group. Patient data are provided in Table 1. Eighty-eight study patients (69%) received oral anticoagulation before inclusion into the study. At the index admission, 18 patients (14%) in the study group had a history of a previous embolism, and six patients (5%) had neurologic deficits. Multivariate analysis of atherosclerotic risks factors (diabetes, hypertension, smoking, hypercholesterolemia) and left ventricular (LV) dysfunction (LVEF <50%) shows patients with dense SEC as having a higher incidence of these risk factors, as compared with patients with faint SEC (110 [86%] vs. 104 [73%], p < 0.01). Table 1 provides patient data. Figure 3 shows the Kaplan-Meier graph for the combined end point (death and embolism) during the observation period.

Table 1. Patient Characteristics (n = 271)

Age (yrs)	62.5 ± 11.3*
Gender (male)	186 (69%)
Previous thromboembolism	41 (15%)
Diabetes mellitus	49 (18%)
Smoking	112 (41%)
Hypertension	143 (53%)
Hypercholesterolemia (>220 mg/dl)	154 (57%)
Embolism during follow-up	33 (12%)

*Mean value ± SD.

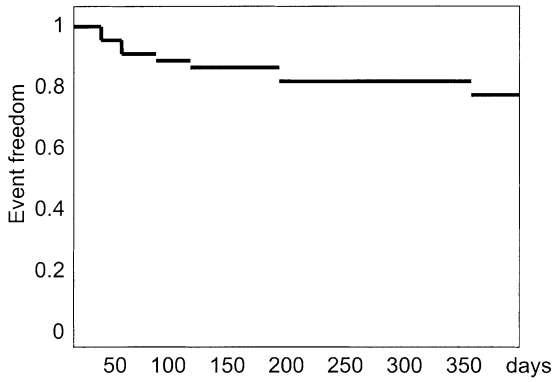

Figure 3. Kaplan-Meier graph for the combined end point (death and embolism) during the 12-month observation period.

Echocardiography. Measurements of LV and LA dimensions, LVEF, and LAA peak emptying velocities are given in Table 2. At the index admission, the mean SEC degree was 2.5 ± 0.9, and the mean peak emptying velocity of the LAA was 0.27 ± 0.15 m/s. When comparing SEC degree and LAA emptying velocities with the Wilcoxon signed rank test, there is a significant match (p < 0.0001). Interobserver agreement for SEC score was kappa = 0.87 and for LAA emptying velocities kappa = 0.92. Twelve patients (9%) had a patent foramen ovale. Ten patients had aortic plaques >4 mm, and 86 patients had plaques <4 mm. None of the patients had mobile aortic atheroma. Patients with and without aortic plaque >4 mm did not differ in terms of the incidence of embolic events. None of the patients had thrombi in the LA or LAA at entry in the study or during the observation period. Echocardiographic data are listed in Table 2.

Cranial MRI and neurologic examination. Ten study patients had old focal diffusion abnormalities at the index admission. During the 12-month follow-up period, 22 (17%) of 128 patients manifested acute cerebral diffusion abnormalities in a pattern consistent with embolic lesions. The size of the embolic lesions was <5 mm in 17 lesions, 5 to 10 mm in 3 lesions, and >10 mm in 2 lesions. The affected vascular territories were superficial middle cerebral

Table 2. Echocardiographic Data

LAV (cm^3)	99 ± 71
LVVD (cm^3)	126 ± 38
LVEF (%)	56 ± 14
SEC (grade)	1.9 ± 0.9
LAAV (m/s)	0.37 ± 0.18
LAAV ≤0.2 m/s	35 (13%)
Persistent foramen ovale (n)	26 (10%)

Data are presented as the mean value ± SD or number (%) of patients.

LAAV = left atrial appendage peak emptying velocity; LAV = left atrial volume; LVEF = left ventricular ejection fraction; LVVD = left ventricular end-diastolic volume; SEC = spontaneous echo contrast.

arteries (n = 20) and deep middle cerebral arteries (n = 2). No diffusion abnormalities in border zone areas or diffuse diffusion abnormalities were noted. Eleven (9%) of 43 patients had new MRI findings at the 1-month follow-up, 15 (12%) at the 3-month follow-up, 20 (16%) at 6-month follow-up, and 22 (17%) at 12-month follow-up.

Three patients developed clinically apparent neurologic deficits and cerebral infarctions, as documented by cranial MRI, and two of these patients died from stroke. A total of eight patients died during the observation period. Nineteen patients had clinically unapparent cerebral embolism, as documented by diffusion defects. In the control group, five (4%) had clinical silent cerebral embolism, as documented by cranial MRI during the observation period. In the patients with silent cerebral embolism, follow-up conventional MRI was performed three months after the event, as documented by cranial MRI. The patients developed a focal signal hyperattenuation on the T2-weighted and FLAIR imaging in the region corresponding to the original index lesion, indicating infarcted brain tissue.

Carotid artery disease. Seventeen study patients had carotid stenosis <50%. None of them had a cerebral lesion during the observation period.

Anticoagulation. Eighty-eight study patients (69%) were anticoagulated effectively at the index admission. Ten patients with effective anticoagulation at admission had a cerebral embolism during the follow-up period. During the observation period, the average INR was 2.3 ± 0.3. Eighty-eight patients (69%) were anticoagulated effectively during the 12-month follow-up period, and 40 (31%) ineffectively. The INR at the date of the event was 2.2 ± 0.4. At the time of the event, eight patients (29%) were not anticoagulated effectively (INR <2.0). Patients with and without effective anticoagulation at the time of the event or during the entire follow-up period did not differ in terms of the incidence of embolic events.

Table 3. Comparison of Echocardiographic Data

	Study Patients (n = 128)	Controls (n = 143)
Age (yrs)	63.6 ± 8.7	60.7 ± 12.4
Gender (male)	86 (67%)	100 (70%)
Diabetes mellitus	23 (18%)	26 (18%)
Hypertension	61 (48%)	82 (57%)
Mean INR	2.3 ± 0.3	2.3 ± 0.4
LAV (cm^3)	116 ± 97*	84 ± 26*
LVVD (cm^3)	131 ± 49	122 ± 25
LVEF (%)	55 ± 16	57 ± 13
SEC (grade)	2.5 ± 0.9†	1.4 ± 0.5†
LAAV (m/s)	0.30 ± 0.20†	0.44 ± 0.16†
Persistent foramen ovale (n)	12 (9%)	14 (10%)
Aortic plaque >4 mm	10 (8%)	7 (5%)
Aortic plaque <4 mm	86 (67%)	83 (58%)
Embolism during follow-up	28 (22%)	5 (4%)

*p < 0.001. †p < 0.0001. Data are presented as the mean value ± SD or number (%) of patients.
INR = international normalized ratio; other abbreviations as in Table 2.

Table 4. Comparison of Echocardiographic Data

	Patients With Embolism (n = 33)	Patients Without Embolism (n = 238)
LAV (cm^3)	121 ± 52	115 ± 11
LVVD (cm^3)	139 ± 57	129 ± 47
LVEF (%)	55 ± 18	54 ± 15
SEC (grade)	2.8 ± 1.1*	1.8 ± 0.8*
LAAV (m/s)	0.22 ± 0.11*	0.38 ± 0.17*
LAAV ≤0.2 m/s	21 (42%)*	14 (6%)*
Persistent foramen ovale	4 (14%)	8 (8%)

*p < 0.0001. Data are presented as the mean value ± SD or number (%) of patients.
Abbreviations as in Table 2.

Predictors of cerebral embolism. Patients with cerebral embolism had significantly lower peak emptying velocities of the LAA (0.2 ± 0.1 m/s vs. 0.3 ± 0.2 m/s, p < 0.001), denser SEC (3.1 ± 0.8 vs. 2.4 ± 0.9, p < 0.0001), and more commonly a positive history of thromboembolic events (9 [32%] vs. 12 [12%], p = 0.02). Table 3 shows the echocardiographic data comparing patients with dense SEC and controls. When matching the combined end point of embolism and/or death and SEC degree by the Wilcoxon signed rank test definition, there is significant concordance (p < 0.0001). In Table 4, echocardiographic data comparing study patients with and without embolic event during the observation period are provided. Multivariate analysis of atherosclerotic risk factors and LV dysfunction comparing patients with and without embolic events shows people with an embolic event to have a higher incidence regarding these risk factors (31 [94%] vs. 183 [77%], p = 0.02). When comparing study patients with and without an embolic event or patients with silent and clinically apparent embolism, no significant difference in atherosclerotic risk factors and LV dysfunction could be found. Table 5 provides a comparison of patients with silent and clinically apparent embolic events.

DISCUSSION

One of the most important complications of AF is thromboembolism—in particular, cerebral embolism. It was shown that oral anticoagulation could reduce the risk of cerebral embolism substantially (15,16). More recent studies have shown that patients with echocardiographic risk factors

Table 5. Patients With Primary End Points—Apparent Versus Silent

	Apparent Embolism (n = 9)	Silent Embolism (n = 19)
LAV (cm^3)	123 ± 41	120 ± 59
LVVD (cm^3)	152 ± 88	131 ± 29
LVEF (%)	61 ± 22	51 ± 14
SEC (grade)	3.1 ± 0.9	2.6 ± 1.1
LAAV (m/s)	0.21 ± 0.17	0.23 ± 0.11
LAAV ≤0.2 m/s	7 (78%)	14 (74%)
Persistent foramen ovale	0	4 (21%)

Data are presented as the mean value ± SD.
Abbreviations as in Table 2.

(17–19) have an elevated risk of thromboembolism. Dense SEC and low peak emptying velocities of the LAA have been identified as important risk factors for an elevated risk of thromboembolism (17,19). However, there are little prospective data available on the risk of thromboembolism in patients with SEC receiving continued oral anticoagulation. Furthermore, there are no studies available assessing the incidence of cerebral embolism serially by modern cranial MRI techniques.

The primary finding of our study is that patients with nonvalvular AF and dense SEC have an increased risk of clinically apparent cerebral embolism or death (7%), despite continued oral anticoagulation. Furthermore, our study showed that those patients have a particularly high probability of silent cerebral embolism (15%), as assessed by serial cranial MRI.

The finding of a 2% incidence of clinically apparent embolism is in accordance with the data of the Stroke Prevention in Atrial Fibrillation (SPAF-III) trial (18), demonstrating an incidence of 1.9% in patients with AF and adjusted dose warfarin. Furthermore, patients with dense SEC were identified as having an increased risk of thromboembolic events (17).

The mean INR level in our study cohort was 2.3, whereas the INR level was 2.4 in the SPAF-III trial. An INR of 2.0 to 3.0, with a target INR of 2.5, is recommended by the current guidelines of the American College of Cardiology (20). The data of our study raise concern as to the effectiveness of this approach. Whether the addition of acetylsalicylic acid to oral anticoagulation will lower the incidence of cerebral embolism is debated (20). In our study, patients did not receive additional acetylsalicylic acid. Furthermore, there is concern that the addition of acetylsalicylic acid will raise the incidence of bleeding complications (18,21).

Our finding of a high incidence of clinical silent cerebral embolism strengthens the assumption that patients with SEC are at a particular high risk of embolism, despite attempts at effective oral anticoagulation. We and other study groups have previously demonstrated that cerebral lesions, as demonstrated by cerebral MRI, result in permanent brain damage (8–10). This was also demonstrated in this study.

Another important finding of our study was that patients with and without effective oral anticoagulation did not differ in terms of the incidence of cerebral embolism. A possible explanation may be that an INR target of 2.5 was not sufficient to prevent cerebral embolism. On the other hand, it may also be possible that fluctuations in the level of the INR were missed, despite serial control of INR levels, and lower levels were associated with events. In this respect, it is important to note that 15 of 22 events occurred during the first three months of the observation period. Because the target dose is adjusted during the first month, it is quite possible that patients with SEC are at particularly high risk during this period.

The results of our study also demonstrate that the intensity of SEC and the level of the peak emptying velocities of the LAA were predictors of cerebral embolism. The SEC was related to a low flow phenomenon in the LA and its appendage. Thus, it is possible that patients with very dense SEC or low peak emptying velocities of the LAA are at particularly high risk of embolism. This finding is in concordance with other studies showing that patients with peak emptying velocities of the LAA <0.2 m/s or dense SEC have a high risk of embolism.

Clinical implications. These correlations of clinical and TEE findings support the thesis of a relationship between LA blood flow stasis and stroke risk in patients with permanent nonvalvular AF.

Study limitations. The number of patients investigated was relatively small. However, patient data were assessed on a prospective basis.

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