Left Atrial Appendage Thrombus Is Not Uncommon in Patients With Acute Atrial Fibrillation and a Recent Embolic Event: A Transesophageal Echocardiographic Study

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Objectives. The objective of this study was to determine the frequency of left atrial thrombus in patients with acute atrial fibrillation.

Background. It is commonly assumed but unproved that left atrial thrombus in patients with atrial fibrillation begins to form after the onset of atrial fibrillation and that it requires ≥3 days to form. Thus, patients with acute atrial fibrillation (i.e., <3 days) frequently undergo cardioversion without anticoagulation prophylaxis.

Methods. Three hundred seventeen patients (250 men, 67 women; mean [±SD] age 64 ± 12 years) with acute (n = 143) or chronic (n = 174) atrial fibrillation were studied by two-dimensional transesophageal echocardiography.

Results. Left atrial appendage thrombus was present in 20 patients (14%) with acute and 47 patients (27%, p < 0.01) with chronic atrial fibrillation. In patients with a recent embolic event, the frequency of left atrial appendage thrombus did not differ between those with acute (5 [21%] of 24) and those with chronic (12 [23%] of 52, p = NS) atrial fibrillation. Patients with acute versus chronic atrial fibrillation, respectively, did not differ (p = NS) in mean age (64 ± 13 vs. 65 ± 11 years), frequency of concentric left ventricular hypertrophy (32% vs. 26%), hypertension (32% vs. 41%), coronary artery disease (35% vs. 39%), congestive heart failure (43% vs. 48%), mitral stenosis (4% vs. 7%) or mitral valve replacement (1.4% vs. 6%). The minimally detectable difference in proportions between patients with acute and chronic atrial fibrillation based on a power of 0.80 and base proportion of 0.20 was 14%.

Conclusions. Left atrial thrombus does occur in patients with acute atrial fibrillation <3 days in duration. The frequency of left atrial thrombus in patients with recent emboli is comparable between those with acute and chronic atrial fibrillation. These data suggest that patients with acute atrial fibrillation for <3 days require anticoagulation prophylaxis or evaluation by transesophageal echocardiography before cardioversion and should not be assumed to be free of left atrial thrombus.

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Atrial fibrillation is a potentially serious and common cardiac arrhythmia that occurs in 2% to 4% of adults >60 years of age (1,2). Atrial fibrillation is associated with a high risk of systemic embolism, congestive heart failure and death (3–5). The appropriate management of patients with atrial fibrillation to reduce morbidity and mortality remains a clinical challenge. Although unproved, the postulate that converting atrial fibrillation to sinus rhythm will reduce morbid events and prolong survival has shaped the clinical management of these patients (6). Unfortunately, cardioversion of atrial fibrillation is associated with a small but significant incidence of systemic embolism (7–10). Although no definitive study has been reported, several earlier (7) and recent (8–10) studies support the recommendation of the American College of Chest Physicians

for anticoagulation in patients before elective cardioversion of atrial fibrillation of ≥3 days in duration (11).

The rationale for not recommending anticoagulation before cardioversion in patients with atrial fibrillation of <3 days in duration is based on the assumption that a left atrial thrombus forms after the onset of atrial fibrillation and requires 48 to 72 h to form. However, we are unaware of any studies reporting the frequency of left atrial thrombus in patients with atrial fibrillation of <3 days in duration. Recent studies utilizing transesophageal echocardiography have demonstrated left atrial thrombus in 12% to 26% of patients with atrial fibrillation, but none of these studies has addressed the frequency of left atrial thrombus in patients with atrial fibrillation of <3 days in duration (12–14). In addition, it has recently been shown that left atrial spontaneous echocardiographic contrast is an independent risk factor for systemic embolism (15,16). The frequency of spontaneous echocardiographic contrast in patients with atrial fibrillation of <3 days in duration is unknown. Therefore, the purpose of this study was to determine the frequency of left atrial thrombus and spontaneous echocardiographic contrast in patients with acute

atrial fibrillation. Patients with acute and chronic atrial fibrillation were compared to gain insight into potential differences in clinical and echocardiographic predictors of left atrial thrombus.

Methods

Patients. Three hundred seventeen patients (250 men, 67 women; mean [±SD] age 64 ± 12 years, range 25 to 87) who met inclusion and exclusion criteria were enrolled from August 1989 to December 1993. Inclusion criteria included atrial fibrillation documented by a 12-lead electrocardiogram (ECG), referral to the laboratory for a clinically indicated transesophageal echocardiographic study and atrial fibrillation at the time of transesophageal echocardiography. Exclusion criteria included inability to determine duration of atrial fibrillation or technically inadequate assessment of the left or right atria by transesophageal echocardiography. The duration of atrial fibrillation was determined clinically by the abrupt onset of new or worsening persistent cardiovascular symptoms (i.e., palpitations, dyspnea, angina, dizziness), electrocardiographically documented onset of atrial fibrillation while in the hospital or review of previous ECGs in patients with long-standing or paroxysmal atrial fibrillation. The duration of atrial fibrillation in patients with paroxysmal arrhythmia was determined as the aggregate duration of previous and present episodes. Atrial fibrillation of <3 days in duration and of new onset was defined as acute (n = 143) and that of ≥3 days in duration defined as chronic (n = 174).

Additional clinical information obtained from all patients included the presence or absence of systemic hypertension (i.e., systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg, or both, requiring treatment), coronary artery disease (documented by previous cardiac catheterization, myocardial infarction or classic angina pectoris), congestive heart failure or recent (i.e., within 7 days of transesophageal echocardiography) systemic emboli (i.e., nonhemorrhagic and nonlacunar stroke, transient ischemic attack or peripheral emboli). Cerebrovascular accident or stroke was defined as the abrupt onset of a focal motor, sensory, cranial nerve, visual or speech deficit confirmed by examination of a neurologist and lasting ≥24 h. Transient ischemic attack was defined as sudden onset of a focal neurologic deficit lasting <24 h and in the distribution of a major cerebral artery. In general, in patients presenting with cerebrovascular accident or transient ischemic attack, computed tomographic brain scan was done within 48 h and repeated 7 days later. Lacunar infarction was defined as either a head computed tomographic scan showing a <1.5-cm hypodense deep infarction or clinical findings typical of lacunar infarction (i.e., pure motor or sensory stroke, dysarthria–incoordination hand syndrome, etc.) and systemic hypertension if there was no computed tomographic brain scan lesion. Peripheral systemic embolus was defined as abrupt occlusion of an artery supplying the legs, arms or viscera documented by examination, noninvasive Doppler imaging, angiography or surgical inspection.

Aspirin use and anticoagulation status were determined.

Anticoagulation was considered therapeutic if prothrombin time was ≥1.5 times normal or activated partial thromboplastin time was ≥2 times normal in patients receiving warfarin or heparin, respectively. Seventy-six patients had a systemic embolic event. The predominant etiologies predisposing to atrial fibrillation were coronary artery disease (n = 99), systemic hypertension (n = 49), severe mitral regurgitation (n = 33), idiopathic dilated cardiomyopathy (n = 26), alcohol abuse (n = 21), mitral stenosis (n = 18), valvular heart disease (n = 12) requiring prior mitral valve (n = 8) or aortic valve (n = 4) prosthetic valve replacement, acute exacerbation of chronic obstructive pulmonary disease (n = 12), severe tricuspid regurgitation (n = 7), mitral valve prolapse (n = 5), pulmonary emboli (n = 5), hypertrophic obstructive cardiomyopathy (n = 3), sepsis (n = 3), myocarditis (n = 2), severe aortic insufficiency (n = 2), aortic stenosis (n = 1), constrictive pericarditis (n = 1), postoperative state (n = 3), hyperthyroidism (n = 1) and congenital heart disease (n = 3). Eleven patients (3.5%) had no identifiable cardiac or noncardiac etiology of atrial fibrillation (i.e., lone atrial fibrillation).

Transesophageal echocardiography. Transesophageal echocardiography was performed with commercially available echocardiography machines (models 77020 and Sonos 1500, Hewlett-Packard, Co.) with a 5.0-MHz, 64-element phased-array monoplane scope (n = 160), 5.0-MHz, 48-element phased-array biplane scope (n = 148), or a 5.0-MHz, 64-element phased-array omniplane scope (n = 9). After insertion of the scope, a comprehensive sequence of two-dimensional views was obtained, and color flow and spectral Doppler studies were performed in a manner similar to previous descriptions (17–19). Transesophageal echocardiographic studies included imaging of all valves and cardiac chambers. Gain settings were adjusted to minimize gray-noise artifact when assessing for spontaneous echocardiographic contrast (20). A detailed assessment of the left and right atrial chambers and their appendages was performed to delineate intracardiac thrombus using multiple views. Thrombus was assessed for mobility. Transesophageal M-mode echocardiography was performed (21). Contrast (i.e., agitated saline injection) transesophageal echocardiography was performed to assess the patency of the foramen ovale membrane (22).

Transthoracic echocardiography. Transthoracic echocardiography was performed with commercially available echocardiographic systems (models 77020 and Sonos 1500, Hewlett-Packard) using a 2.5-MHz transducer. Comprehensive transthoracic M-mode, two-dimensional, color-flow and spectral Doppler echocardiography were performed from the standard parasternal, apical and subcostal acoustic windows. Transthoracic and transesophageal echocardiographic studies were performed the same day and recorded on half-inch videotape for subsequent review and analysis.

Echocardiographic analysis. Transesophageal and transthoracic echocardiograms were analyzed in blinded manner. Echocardiographic studies were analyzed by investigators uninformed of clinical data. Quantitative M-mode or two-dimensional echocardiographic measurements were made by a

single echocardiographer. Qualitative assessment of echocardiograms was done by two experienced echocardiographers with results reached by consensus. M-mode transthoracic echocardiographic measurements of left atrial and end-diastolic (i.e., peak of QRS R wave) left ventricular diameters and septal and posterior wall thicknesses were made according to the American Society of Echocardiography recommendations (23). Analogous transesophageal M-mode echocardiographic measurements of the end-diastolic left ventricular diameter and wall thicknesses were made in the case of a technically difficult transthoracic echocardiographic study. Left ventricular mass was calculated from M-mode echocardiography by means of the modified formula of Devereux et al. (24). Left ventricular hypertrophy was considered present if left ventricular mass divided by body surface area was ≥ 134 g/m^2 in men or ≥ 110 g/m^2 in women. Left ventricular hypertrophy was further characterized as concentric or eccentric if the posterior wall thickness times 2 was $\geq 45\%$ or $<45\%$ of the left ventricular end-diastolic diameter, respectively. Qualitative determination of left ventricular ejection fraction was made using two-dimensional transthoracic echocardiography or transesophageal echocardiography if transthoracic echocardiography was technically inadequate. Left and right atrial chambers were assessed for the presence of spontaneous echocardiographic contrast and thrombus. Care was taken to differentiate pectinate muscle mimicking thrombus from true thrombus as previously described (25).

Statistical analysis. All results are mean value $\pm$ 1 SD or a proportion of the population size. Potential differences in continuous variables among groups were assessed by unpaired Student t test. A chi-square analysis with continuity correction was used to assess for potential differences in proportions among groups. A multivariate stepwise regression analysis with dummy variables for the presence (1) or absence (0) of discrete variables was used to assess for independent predictors of the presence of left atrial thrombus or embolic event. A power analysis yielded the minimally detectable difference in proportions based on the sizes of the groups, and assuming alpha 0.05, base proportion of 0.20 and a power of 0.80 (26). A p value <0.05 was considered statistically significant.

Results

Acute versus chronic atrial fibrillation. One hundred forty-three patients had acute and 174 patients had chronic atrial fibrillation (Table 1). Mean duration of atrial fibrillation at the time of transesophageal echocardiography in patients with acute atrial fibrillation was 1.6 $\pm$ 0.8 days (range 0 to <3 days) and 890 $\pm$ 1,279 days (range 3 days to 25 years) in patients with chronic atrial fibrillation. In patients with acute atrial fibrillation, duration of atrial fibrillation was ≤ 2 days in 127 patients and >2 to <3 days in 16. Patients with acute and chronic atrial fibrillation did not differ in terms of age or frequency of systemic hypertension, congestive heart failure or coronary artery disease. Ten patients with chronic and no patients with acute atrial fibrillation had documented paroxys-

Table 1. Clinical and Echocardiographic Variables in Patients With Acute and Chronic Atrial Fibrillation

	Acute AF (n = 143)	Chronic AF (n = 174)	p Value
Age (yr)	64 ± 13	65 ± 11	0.78
Hypertension	46 (32%)	71 (41%)	0.14
Congestive HF	61 (43%)	83 (48%)	0.43
Coronary disease	50 (35%)	67 (39%)	0.59
Lone AF	9 (6%)	2 (1%)	0.029
Anticoag pre-TEE	34 (24%)	73 (42%)	0.001
Anticoag ≥ 3 wk pre-TEE	3 (2%)	54 (31%)	0.0001
Aspirin daily	15 (10%)	20 (11%)	0.92
LA/LAA-thrombus	20 (14%)	47 (27%)	0.0072
LA-SEC	56 (39%)	100 (57%)	0.0017
RA/RAA-thrombus	3 (2%)	2 (1%)	0.82
RA-SEC	26 (18%)	46 (26%)	0.11
MR ≥ moderate	47 (33%)	78 (45%)	0.04
Mitral stenosis	6 (4%)	12 (7%)	0.43
MV replacement	2 (1.4%)	10 (6%)	0.085
LVEF ≤40%	40 (28%)	68 (39%)	0.05
LA diameter (cm)	4.21 ± 1.04	4.70 ± 1.03	0.0001
Concentric LVH	46 (32%)	45 (26%)	0.27
Eccentric LVH	23 (16%)	34 (20%)	0.52

Data presented are mean value ± SD or number (%) of patients. AF = atrial fibrillation; Anticoag = systemic anticoagulation; HF = heart failure; LA = left atrial; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MR = mitral regurgitation; MV = mitral valve; RA = right atrial; RAA = right atrial appendage; SEC = spontaneous echocardiographic contrast; TEE = transesophageal echocardiography.

mal atrial fibrillation. Although a greater percent of patients with left atrial thrombus were found by transesophageal echocardiography among those with chronic (47 patients, or 27%) than with acute (20 patients, or 14%, p $<$ 0.01) atrial fibrillation, a clinically important percent of patients with acute atrial fibrillation had left atrial thrombus.

In patients with acute atrial fibrillation, left atrial thrombus was confined to the left atrial appendage in 19 patients and to the left atrial cavity and appendage in 1 (Fig. 1). In 7 of 20 patients with acute atrial fibrillation and left atrial thrombus, the onset of atrial fibrillation was documented electrocardiographically in hospital. Of these seven patients, five had mobile thrombus and two had immobile thrombus. In one of the patients with immobile thrombus, the left atrial appendage cavity was completely filled with thrombus (Fig. 2). Case examples of patients with atrial thrombus are shown in Figures 1–3. In patients with acute atrial fibrillation, the percent of patients with left atrial thrombus did not differ between those with atrial fibrillation ≤ 2 days (18 [14%] of 127) and >2 to <3 days (2 [12.5%] of 16, p = NS) in duration. In patients with chronic atrial fibrillation, 41 had isolated left atrial appendage thrombus, 5 had thrombus of the left atrial cavity and appendage, and 1 had a thrombus confined to the left atrial cavity. Left atrial spontaneous echocardiographic contrast, delineated using transesophageal echocardiography, was more common in patients with chronic (57%) than in those with acute (39%, p $<$ 0.002) atrial fibrillation. Right atrial thrombus was uncommon and did not differ in frequency between patients with acute
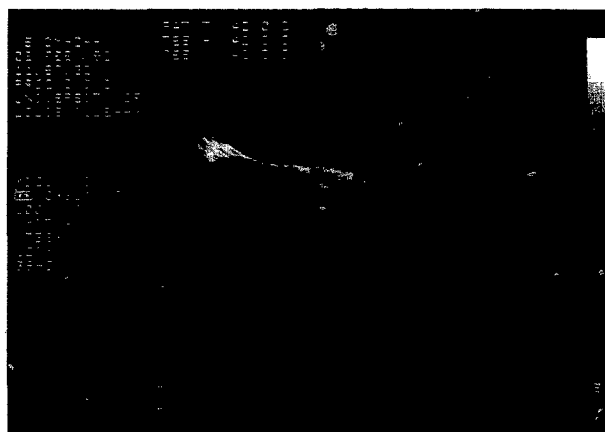
Figure 1. Two-dimensional transesophageal echocardiography in a 70-year old man with acute atrial fibrillation and associated peripheral embolus showing a mobile left atrial thrombus (**arrow**) and mobile thrombus near opening (**upper arrowhead**) and midportion (**lower arrowhead**) of left atrial appendage. AO = aorta; LA = left atrium; PA = pulmonary artery.
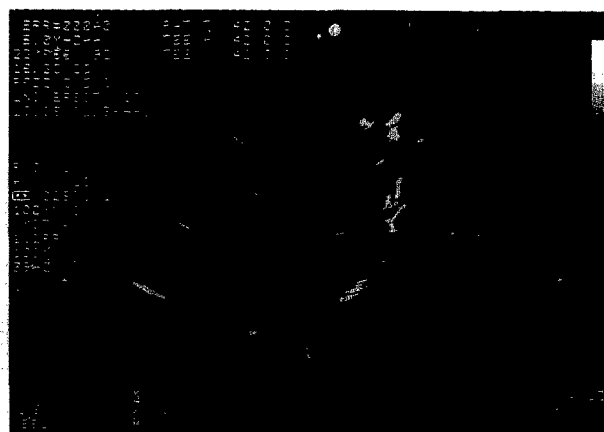

Figure 3. Two-dimensional transesophageal echocardiography in a 78-year old woman with acute atrial fibrillation and peripheral embolus showing typical location of a mobile thrombus (**arrow**) confined to the left atrial appendage, not the left atrium (LA). Other abbreviations as in Figure 1.

(2%) and chronic (1%, p = NS) atrial fibrillation. Of the five patients with right atrial thrombus, four had isolated right atrial appendage thrombus, and one had a right atrial appendage and right atrial cavity thrombus. None of these patients had a pulmonary embolus. All right atrial thrombi were attached to atrial endocardial surface and not in transit. Right atrial spontaneous echocardiographic contrast was less frequent than left atrial spontaneous echocardiographic contrast and did not differ in frequency between patients with acute (18%) and chronic (26%, p = NS) atrial fibrillation. Transthoracic echocardiography failed to delineate left or right atrial thrombus or spontaneous echocardiographic contrast in any patient.

Figure 2. Two-dimensional transesophageal echocardiography in an 84-year old woman with acute atrial fibrillation caused by coronary artery disease showing an immobile dense thrombus (**arrows**) completely filling a dilated left atrial appendage. The onset of atrial fibrillation was documented electrocardiographically. Abbreviations as in Figure 1.

A greater percent of patients with chronic (42%) than acute (24%, p < 0.002) atrial fibrillation had systemic anticoagulation before echocardiography. Only three patients (2%) with acute atrial fibrillation were receiving long-standing (i.e., ≥3 weeks) anticoagulation. However, 54 (31%) patients with chronic atrial fibrillation were receiving long-standing anticoagulation. In patients with anticoagulation, the duration of anticoagulation was significantly shorter in patients with acute (4 ± 8 days) than chronic (598 ± 1,099 days, p < 0.001) atrial fibrillation. Daily aspirin use did not differ between the two groups and was infrequent.

The percent of patients with mitral stenosis or previous prosthetic mitral valve replacement surgery did not differ between patients with acute and chronic atrial fibrillation and was small. Moderate or greater mitral regurgitation was common in both groups but more frequent in patients with chronic (45%) than acute (33%, p < 0.05) atrial fibrillation. Moderate or greater impairment in global left ventricular function (i.e., left ventricular ejection fraction ≤40%) was more common in patients with chronic atrial fibrillation. The frequency of concentric or eccentric left ventricular hypertrophy did not differ between groups. Patients with chronic atrial fibrillation had a larger left atrial diameter than those with acute atrial fibrillation. Lone atrial fibrillation was uncommon in both groups but was more frequent in patients with acute (6%) than in chronic (1%, p < 0.05) atrial fibrillation. One of 11 patients with lone atrial fibrillation had a left atrial appendage thrombus. This patient had chronic atrial fibrillation.

Acute and chronic atrial fibrillation: influence of systemic emboli. Twenty-four patients with acute and 52 with chronic atrial fibrillation had a recent systemic embolus, defined as a nonhemorrhagic and nonlacunar cerebrovascular accident (n = 42), transient ischemic attack (n = 22) or peripheral embolus (n = 12) (Table 2). In patients without an embolic event, left atrial thrombus was twice as frequent in patients

Table 2. Echocardiographic Variables and Anticoagulation Status in Patients With Acute and Chronic Atrial Fibrillation With and Without Recent Systemic Emboli

	Embolic Group			Nonembolic Group		
	Acute AF (n = 24)	Chronic AF (n = 52)	p Value	Acute AF (n = 119)	Chronic AF (n = 122)	p Value
Anticoag pre-TEE	2 (8%)	24 (46%)	0.002	32 (27%)	49 (40%)	0.04
Anticoag ≥ 3 weeks pre-TEE	0 (0%)	20 (39%)	0.001	3 (3%)	34 (28%)	0.0001
Aspirin daily	2 (8%)	9 (17%)	0.49	13 (11%)	11 (9%)	0.78
LA/LAA-thrombus	5 (21%)	12 (23%)	0.94	15 (13%)	35 (29%)	0.0035
LA-SEC	10 (42%)	30 (58%)	0.29	46 (39%)	70 (57%)	0.0054
RA/RAA-thrombus	0 (0%)	1 (2%)	0.69	3 (3%)	1 (1%)	0.60
RA-SEC	4 (17%)	17 (33%)	0.24	22 (18%)	29 (24%)	0.40
MR ≥ moderate	10 (42%)	18 (35%)	0.74	37 (31%)	60 (49%)	0.0063
Mitral stenosis	1 (4%)	3 (6%)	0.79	5 (4%)	9 (7%)	0.44
MV replacement	0 (0%)	4 (8%)	0.40	2 (2%)	6 (5%)	0.30
LVEF ≤40%	3 (13%)	18 (35%)	0.084	37 (31%)	50 (40%)	0.14

Data presented are number (%) of patients. Abbreviations as in Table 1.

with chronic (29%) than acute (13%, p < 0.005) atrial fibrillation. Similarly, left atrial spontaneous echocardiographic contrast was more frequent in patients with chronic than acute (57% vs. 39%, p < 0.01) atrial fibrillation without recent embolic event. However, in subjects with a recent embolic event, the frequency of left atrial thrombus or left atrial spontaneous echocardiographic contrast did not differ between patients with acute and chronic atrial fibrillation. Right atrial thrombus was uncommon and did not differ in frequency among the groups. The presence of right atrial spontaneous echocardiographic contrast did not differ between patients with acute and chronic atrial fibrillation with or without a recent embolic event. Anticoagulation of any duration or ≥3 weeks before transesophageal echocardiography was significantly more common in patients with chronic than acute atrial fibrillation with or without a recent embolic event. Daily aspirin use was infrequent and did not differ among the groups. The frequency of mitral stenosis, previous mitral valve replacement or moderate or greater impairment in left ventricular function (i.e., left ventricular ejection fraction ≤40%) did not differ between patients with acute and chronic atrial fibrillation with or without a recent embolic event. Mitral regurgitation of moderate or greater severity was common in all groups. In patients with a recent embolic event (acute atrial fibrillation, n = 24 vs. chronic atrial fibrillation, n = 52), the presence of other potential cardiac etiologies of emboli did not differ, such as a patent foramen ovale membrane (8 patients, or 33% vs. 12 patients, or 23%, p = NS) or left heart vegetation (2 patients, or 8% vs. 3 patients, or 6%, p = NS).

Mobility of thrombus and systemic emboli: acute versus chronic atrial fibrillation. In patients with left atrial thrombus, mobile thrombus was equally common in patients with acute (10 [50%] of 20) and chronic (23 [49%] of 47, p = NS) atrial fibrillation. In patients with acute atrial fibrillation, mobile left atrial thrombus was seen more commonly in those with (5 [100%] of 5) than in those without (5 [33%] of 15, p < 0.05) an embolic event. However, in patients with chronic atrial

fibrillation, the frequency of mobile left atrial thrombus did not differ between patients with (8 [67%] of 12) and without (15 [43%] 35, p = NS) an embolic event. Multivariate analysis showed that in patients with acute atrial fibrillation, mobile left atrial thrombus (p < 0.05), congestive heart failure (p < 0.02), coronary artery disease (p < 0.05) and left ventricular ejection fraction ≤40% (p < 0.05) were independent predictors of an embolic event. No appropriate clinic   hocardiographic variable was a predictor of an embolic event in patients with chronic atrial fibrillation. In p.   with chronic atrial fibrillation with a left atrial thrombus (n = 47), 20 were receiving therapeutic long-term anticoagulation for a mean duration of 1,082 ± 1,536 days (range 60 to 4,745). Of these 20 patients, 10 had mobile left atrial thrombus. Only 1 of 20 patients in patients with acute atrial fibrillation with left atrial thrombus was receiving long-term anticoagulation. This patient had an immobile thrombus and a prosthetic mitral valve.

Predictors of left atrial thrombus. Multivariate analysis was performed in an attempt to identify clinical and transthoracic echocardiographic indexes that would predict the presence of left atrial thrombus on transesophageal echocardiography in patients with acute or chronic atrial fibrillation. Mitral stenosis (p < 0.01) and left ventricular ejection fraction ≤40% (p < 0.02) were independent predictors of the presence of left atrial thrombus in patients with acute atrial fibrillation. Age, gender, hypertension, congestive heart failure, coronary artery disease, recent embolic event, lack of anticoagulation before transesophageal echocardiography, left atrial diameter, prosthetic mitral valve replacement and lack of moderate or greater mitral regurgitation were not independent predictors of left atrial thrombus in patients with acute fibrillation. Of the 20 patients with acute atrial fibrillation and left atrial thrombus, 10 had a left ventricular ejection fraction ≤40% (i.e., sensitivity 50%), and 3 had mitral stenosis (i.e., sensitivity 15%). On the basis of transthoracic echocardiographic findings, 65% (13 of 20) of patients with acute atrial fibrillation and left atrial thrombus would have been correctly identified as

being at higher risk for the presence of left atrial thrombus. The specificities of left ventricular ejection fraction >40% and no mitral stenosis for no left atrial thrombus in patients with acute atrial fibrillation were 76% (93 of 123) and 98% (120 of 123), respectively. When left atrial spontaneous echocardiographic contrast determined by transesophageal echocardiography was entered into the regression model, it became the only independent predictor of left atrial thrombus (p < 0.0002) in patients with acute atrial fibrillation. Increasing left atrial diameter (p < 0.003) and prosthetic mitral valve replacement (p < 0.005) were the only independent predictors of the presence of left atrial thrombus in patients with chronic atrial fibrillation. The presence of left atrial diameter ≥5.0 cm (n = 27) and/or prosthetic mitral valve (n = 6) in patients with chronic atrial fibrillation and left atrial thrombus was 60% (28 of 47) sensitive for left atrial thrombus. Left atrial diameter <5.0 cm and no prosthetic mitral valve was 85% (108 of 127) specific for no left atrial thrombus in the chronic group. Left atrial spontaneous echocardiographic contrast was not a predictor of left atrial thrombus in subjects with chronic atrial fibrillation.

Power analysis. The minimally detectable difference in proportions with a base proportion of 0.20 was 14% for patients with acute versus chronic atrial fibrillation, 16% for those with acute versus chronic atrial fibrillation with no embolism and 32% for those with acute versus chronic atrial fibrillation with embolism.

Discussion

Although the mechanism of left atrial thrombus formation and subsequent embolization is undoubtedly complex and ill-defined, the postulate that atrial fibrillation must persist >2 to 3 days before left atrial thrombus forms has become widely accepted (11). In addition, it is assumed that left atrial thrombus forms after the onset of atrial fibrillation and embolizes as a result of the dynamic shear forces of the circulation, particularly after return in atrial contraction with resumption of sinus rhythm. Because of these concepts, cardioversion of atrial fibrillation <3 days in duration without anticoagulation prophylaxis is believed to be safe and is commonly performed. However, it is unclear how long it takes for thrombi to form in fibrillating atria and probably depends on multiple factors such as type of underlying heart disease, ventricular function, atrial size and function, and intraatrial coagulability. The results of the present study challenge the widespread opinion that patients with acute atrial fibrillation <3 days in duration are free of left atrial thrombi. Fourteen percent of patients with atrial fibrillation <3 days in duration in the present study had left atrial thrombi. We are unaware of any previous studies reporting the occurrence of left atrial appendage thrombus in patients with atrial fibrillation <3 days in duration.

Left atrial thrombus formation. It is possible that left atrial thrombus forms in patients with atrial fibrillation within 3 days of or before the onset of the arrhythmia. Embolic events may

occur within 2 to 3 days after electrical cardioversion of atrial fibrillation despite lack of atrial thrombus on transesophageal echocardiography before cardioversion (13,27,28). Electrical cardioversion impairs left atrial appendage function and may predispose to thrombus formation (27,29), presumably within days of cardioversion and may account for some cardioversion-related embolism. These data support the notion that thrombus may form in the left atrium within 3 days. Mügge et al. (30) demonstrated left atrial thrombus in 23 patients with sinus rhythm. In such patients, it is possible that left atrial appendage dysfunction may occur despite the presence of left atrial mechanical function and predispose to thrombus formation (31). Although in the present study patients with acute atrial fibrillation were considered to have atrial fibrillation of new onset, it is possible that clinically silent and undocumented paroxysmal episodes of atrial fibrillation may have resulted in left atrial thrombus formation.

Predictors of thrombus. Clinical and echocardiographic predictors of the presence of left atrial thrombus by transesophageal echocardiography differ between patients with acute and chronic atrial fibrillation. In patients with acute atrial fibrillation, impaired left ventricular function and mitral stenosis predispose to left atrial spontaneous echocardiographic contrast. Although the exact mechanism of left atrial spontaneous echocardiographic contrast is unknown, it may relate to stasis of blood flow leading to rouleaux formation by erythrocytes (32). Left atrial spontaneous echocardiographic contrast may lead to the formation of left atrial thrombus (15,20). However, in the present study patients with chronic versus acute atrial fibrillation, left atrial spontaneous echocardiographic contrast was not an independent predictor of left atrial thrombus. In patients with chronic atrial fibrillation, other determinants of left atrial thrombus, such as increasing left atrial size, appear to play a more important role in the formation of left atrial thrombus. Consistent with previous studies (12,14), in the present study a greater predilection for thrombus formation was found in the left atrium than the right atrium. The factors that account for this difference is unknown. Similarly, spontaneous echocardiographic contrast of the right compared with the left atrium was less common. These differences may relate to left versus right atrial size, the narrower shape of the left atrial appendage predisposing to stasis, anatomic and functional differences in venous inflow, left versus right ventricular function, or the presence and type of atrioventricular valve disease.

Thrombus mobility and embolism. Dislodgment of thrombus from the left atrium into the circulation is the likely cause of most systemic embolic episodes in patients with atrial fibrillation. In the present study, mobile compared with immobile left atrial thrombus was an independent predictor of systemic embolism in patients with acute atrial fibrillation, which supports this hypothesis. Multicenter studies have demonstrated the efficacy of anticoagulation with warfarin for decreasing the incidence of ischemic stroke and systemic embolism in patients with atrial fibrillation (33). Despite the use of warfarin, ischemic strokes may occur in patients with

atrial fibrillation. In the present study, 20 of 47 patients with chronic atrial fibrillation and left atrial thrombus were receiving long-standing therapeutic anticoagulation with warfarin. These data suggest that left atrial thrombus may form in patients with atrial fibrillation despite adequate anticoagulation or, once formed, may not resolve after chronic anticoagulation therapy. This phenomenon may partially explain the presence of systemic embolic events in patients with atrial fibrillation despite adequate anticoagulation.

Transthoracic echocardiographic screening. The data from the present study show that transthoracic echocardiography is not an adequate screening test for left atrial thrombus or spontaneous echocardiographic contrast. The finding of left ventricular dysfunction or mitral stenosis in patients with acute atrial fibrillation or of left atrial enlargement in patients with chronic atrial fibrillation is not very useful in predicting a high-risk group for the presence of left atrial thrombus. Left atrial thrombus was predicted in only 65% of patients with acute atrial fibrillation and left atrial thrombus by transthoracic echocardiographic criteria. The potential presence of left atrial thrombus in patients with acute atrial fibrillation and the relatively low sensitivity of transthoracic echocardiography appear to preclude cardioversion without ≥ 3 weeks of anticoagulation prophylaxis or transesophageal echocardiography to exclude the presence of thrombus. The ultimate role of transesophageal echocardiography in such patients before cardioversion remains controversial (12–14, 27–29).

Study limitations. The accuracy of clinically estimating the onset of atrial fibrillation based on patient symptoms has not been extensively tested. One previous study demonstrated that symptoms were predictive of the onset of atrial fibrillation 87.5% of the time (33). It is possible that some of the patients defined as acute in the present study may have had longer-standing atrial fibrillation. However, several patients had documented onset of atrial fibrillation <3 days in duration with findings of left atrial thrombus. In addition, the study is clinically relevant because in practice the onset of atrial fibrillation and the decision to perform electrical cardioversion without anticoagulation are frequently based on clinical presentation and not precise documentation of the onset of atrial fibrillation. The decision to administer anticoagulation may often relate to clinical conditions, such as mitral stenosis, prosthetic heart valve, dilated cardiomyopathy, and not on the basis of atrial fibrillation onset. In the present study, the frequency of left atrial thrombus appears somewhat higher than that in previous studies reporting an incidence of left atrial thrombus in patients with atrial fibrillation of 12% to 13% (12,13). However, the overall frequency of left atrial thrombus in the present study of 21% (67 of 317) is comparable to that of a recent study showing an incidence of 26% (14). In addition, patients with valvular etiologies of atrial fibrillation were not excluded in the present study, unlike some previous studies. Pathologic confirmation of left atrial thrombus was not possible. However, previous studies are consistent with transesophageal echocardiography being a sensitive and specific test for the detection of left atrial thrombus (30,35,36).

Not all cerebrovascular accidents in patients with atrial fibrillation are cardioembolic. A cardioembolic mechanism may exist in as few as 19% to as high as 75% (37–39). Silent or subclinical stroke occurs in atrial fibrillation (40). How these factors may have affected the results of the present study are unknown. Left ventricular function was qualitatively assessed. Previous studies have demonstrated that the qualitative assessment of left ventricular function by two-dimensional echocardiography can be performed with reasonable accuracy. The number of patients with mitral stenosis and prosthetic mitral valves was small, which limits generalization of conclusions to these groups of patients with atrial fibrillation.

Only patients referred to the laboratory for transesophageal echocardiography were enrolled. Therefore, selection bias cannot be excluded. Left atrial appendage function was not assessed in the present study. Such measurements may contribute to the understanding of left atrial thrombus formation in patients with atrial fibrillation (31,41). The definition of the duration of acute fibrillation is arbitrary. The results of the present study would not have changed substantially if ≤ 2 days had been used as the definition of acute atrial fibrillation.

Conclusions. Left atrial thrombus occurs in an important number of patients with acute atrial fibrillation and is usually confined to the left atrial appendage. Mobile left atrial appendage thrombus is an independent risk factor for emboli in patients with acute atrial fibrillation. The hypothesis that patients with atrial fibrillation of <3 days in duration are free of thrombus should no longer be accepted. Anticoagulation prophylaxis should be considered in patients with acute atrial fibrillation before cardioversion, particularly if risk factors for thrombi or emboli exist. Although the role of transesophageal echocardiography in such patients remains unproved, it appears reasonable to perform transesophageal echocardiography before cardioversion in patients with acute atrial fibrillation who are not to receive anticoagulation prophylaxis of 3 weeks in duration.

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