Journal of the American College of Cardiology
Vol. 37, No. 4, 2001

Published by Elsevier Science Inc.
ISSN 0735-1097/01/$20.00
PII S0735-1097(00)01206-7

Endocarditis

Echocardiography Predicts Embolic Events in Infective Endocarditis

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OBJECTIVES The aim of our study was to assess the value of transesophageal echocardiography (TEE) in predicting embolic events (EEs) in a large group of patients with definite endocarditis according to the Duke criteria, including silent embolism.

BACKGROUND The value of echocardiography in predicting embolism in patients with endocarditis remains controversial. Some studies reported an increased risk of embolism in patients with large and mobile vegetations, whereas other studies failed to demonstrate such a relationship.

METHODS Multiplane transesophageal echocardiograms of 178 consecutive patients with definite infective endocarditis (IE) were analyzed. The incidence of embolism was compared with the echocardiographic characteristics (localization, size and mobility) of the vegetations. To detect silent embolism, cerebral and thoraco-abdominal scans were performed in 95% of patients.

RESULTS Among 178 patients, 66 (37%) had one or more EEs. There was no difference between patients with and without embolism in terms of age, gender and left valve involved. On univariate analysis, *Staphylococcus* infection, right-side valve endocarditis and vegetation length and mobility were significantly related to EEs. A significant higher incidence of embolism was present in patients with vegetation length >10 mm (60%, $p < 0.001$) and in patients with mobile vegetations (62%, $p < 0.001$). Embolism was particularly frequent among 30 patients with both severely mobile and large vegetations (>15 mm) (83%, $p < 0.001$). On multivariate analysis, the only predictors of embolism were vegetation length ($p = 0.03$) and mobility ($p = 0.01$).

CONCLUSIONS Our study shows that the presence of vegetations on TEE is predictive of embolism and that the morphologic characteristics of vegetations are helpful in predicting EEs in both mitral and aortic valve IE. It also suggests that early operation may be recommended in patients with vegetations >15 mm and high mobility, irrespective of the degree of valve destruction, heart failure and response to antibiotic therapy. (J Am Coll Cardiol 2001;37:1069–76) © 2001 by the American College of Cardiology

Embolic events (EEs) are a frequent and life-threatening complication of infective endocarditis (IE) (1–4); thus, an accurate prediction of embolic risk in IE may be a desirable goal.

Echocardiography has a well-defined role in the diagnosis and management of IE (5–8), and its value has increased considerably since the introduction of transesophageal echocardiography (TEE), allowing a more complete assessment of vegetation morphology (9–11).

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Several investigators have tried to determine which echocardiographic feature is helpful to evaluate the risk of embolism in patients with IE. Unfortunately, the value of echocardiography in predicting EEs remains controversial. Several investigators do not consider the presence of a vegetation as a specific marker for increased risk of embolism (3,12,13), and the significance of some vegetation characteristics, such as length and mobility, is still unclear. Some studies reported an increased risk of embolism in patients with large (>10 mm) and mobile vegetations (13–15), whereas other studies failed to demonstrate such a relationship (1,3,12,16,17). The causes for these conflicting results are multiple, including the use of transthoracic echocardiography (TTE) versus TEE, various diagnostic criteria for IE and the inclusion or exclusion of patients with subclinical EEs preceding the echocardiographic study.

The aim of our study was to assess the value of echocardiography in predicting EEs in a large group of patients with definite IE according to the Duke criteria (18), as evaluated by multiplane TEE, and including silent EEs.

METHODS

Patients. Among 250 patients referred to our center for suspected IE between September 1993 and January 2000, 178 (133 men and 45 women, mean age 58 ± 15 years) had

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Manuscript received June 21, 2000; revised manuscript received October 25, 2000, accepted December 6, 2000.

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March 15, 2001:1069–76

Abbreviations and Acronyms

BC	= blood culture
CT	= computed tomography
EE	= embolic event
IE	= infective endocarditis
TEE	= transesophageal echocardiography
TTE	= transthoracic echocardiography

a diagnosis of definite IE according to the Duke criteria (18) and formed the study group. Of these 178 patients, 128 had a pathologic confirmation by surgery or autopsy. Blood cultures (BCs) and TEE were performed on all patients.

The bacteriologic and clinical characteristics of the patients are summarized in Table 1 and Table 2. Infective endocarditis involved a native valve in 127 patients, a prosthetic valve in 47 patients and pacemaker leads in 4 patients. In-hospital death occurred in 19 patients (11%).

Surgical management. Surgery was performed in 109 patients (61%). The surgical procedure was valve replacement in 88 patients (81%), including a bioprosthesis in 14%, a mechanical valve in 45% and a homograft in 41%, and conservative surgery (vegetation excision and/or valve repair) in 21 patients (19%). Sixty-nine patients (63% of surgically treated patients) had an operation during the first 10 days after the diagnosis of IE. The indications for early operation included acute aortic or mitral insufficiency in 20 patients (29%), severe heart failure in 15 patients (22%), large persistent vegetation after systemic embolization associated with significant valvular regurgitation in 18 patients (26%) and abscess or perivalvular involvement in 16 patients (23%).

Blood cultures. All patients using an automate (Bactec Becton Dickinson, Sparus, Maryland) had an "endocarditis diagnostic kit," including standard BCs and special samples for isolation of intracellular pathogens and for various specific antibodies (19). Additional BCs were systematically performed if the temperature was >38.5°C, and cultures of the leads and pacemaker device were systematically obtained in patients with IE on pacemaker leads. Major bacteriologic criteria were BCs positive for typical endocardial pathogens or persistently positive for a microorganism consistent with IE. Blood cultures were positive in 146 patients (82%), *Streptococcus* being the most frequent isolated pathogen (Table 1).

Echocardiography. Transesophageal echocardiography was performed on all patients on a Vingmed Diasonics, CFM 800 or System Five. A 5.0-MHz transducer was used for multiplane transesophageal studies. All echocardiographic studies were performed during the acute phase of IE, with no complications. Two experienced echocardiographers independently reviewed the TEE studies without knowledge of the patients' clinical history or subsequent clinical course.

Echocardiographic data were classified by using the Duke echocardiographic criteria (18). Major echocardiographic findings included vegetation, abscess, new partial dehiscence of the prosthetic valve and valvular perforation. As recommended by Durack et al. (18), prosthetic dehiscence and regurgitant murmur had to be documented as new to constitute a major criterion for IE. Minor echocardiographic criteria were considered in the presence of valvular thickening or other echocardiographic abnormalities that fall short of typical valvular vegetations. The usual definitions of perivalvular abscesses were used (18,20,21).

Assessment of vegetations. Vegetation was defined as a fixed or oscillating mass adherent to a leaflet or other cardiac structure with a distinct echogenic structure and independent motion. The lesion had to be visible in multiple views and detectable during the complete cycle. The measurements of vegetations were obtained in various planes, and the maximal length was used. In the presence of multiple vegetations, the largest value was used for analysis.

The mobility of the vegetation was evaluated using a four-point scale (13)—absent = fixed vegetation with no detectable independent motion; low = vegetation with a fixed base but with a mobile free edge; moderate = pedunculated vegetation that remains within the same chamber throughout the cardiac cycle; severe = prolapsing vegetations that cross the coaptation plane of the leaflets during the cardiac cycle.

Definition of EEs. The diagnosis of embolism was based on clinical signs and data derived from noninvasive diag-

Table 1. Occurrence of Different Pathogens and Relation With Embolic Events

	Total Group (n = 178)	Embolism Group (n = 66)	No Embolism Group (n = 112)	p Value*
Streptococci	77 (43.2%)	23 (34.9%)	54 (48.2%)	0.088
Staphylococci	43 (24.2%)	23 (34.9%)	20 (17.8%)	0.023
Enterococci	9 (5.1%)	4 (6%)	5 (4.5%)	0.73
HACEK	6 (3.4%)	3 (4.6%)	3 (2.7%)	0.67
Negative blood cultures	32 (17.9%)	7 (10.6%)	25 (22.3%)	0.068
Q fever	5 (2.8%)	2 (3%)	3 (2.7%)	> 0.99
Others†	6 (3.4%)	4 (6%)	2 (1.8%)	0.196

*Comparison between patients with embolic events and patients without embolism. †Others = Emboli: 3 with *Candida* and 1 with *Gemella morbillorum*; no emboli: 1 with *Corynebacterium difteriae* and 1 with *G. morbillorum*. Data are presented as the number (%) of patients.

HACEK = *Haemophilus, Actinobacillus actinomycotin comitans, Cardiobacterium hominis, Eikenella, Kingella*

Table 2. Clinical Features of Infective Endocarditis in Patients With and Without Embolism

	Total Group (n = 178)	Embolism Group (n = 66)	No Embolism Group (n = 112)	p Value*
Mean age (yrs)	57 ± 15	57 ± 16	57 ± 15	0.73
Patients <65 years old	124 (69.7%)	44 (66.7%)	80 (71.4%)	0.77
Men	133 (74.7%)	53 (80%)	80 (71.4%)	0.55
Predisposing heart disease	121 (68%)	39 (59.1%)	82 (73.2%)	0.053
Previous IE	14 (7.8%)	8 (12.1%)	6 (5.3%)	0.112
IVDA	6 (3.4%)	4 (6.1%)	2 (1.8%)	0.13
Surgical therapy	109 (61.2%)	41 (62.1%)	68 (60.7%)	0.85
In-hospital death	19 (10.7%)	10 (15.2%)	9 (8%)	0.14
IE localization				
Native valve	127 (71.3%)	52 (78.7%)	73 (65.2%)	0.063
Prosthetic valve	47 (26.4%)	12 (18.2%)	34 (30.4%)	0.079
Pacemakers	4 (2.2%)	3 (4.5%)	1 (0.9%)	0.144

*Comparison between patients with embolic events and patients without embolism. Data are presented as the mean value ± SD or number (%) of patients.

IE = infective endocarditis; IVDA = intravenous drug abuse.

nostic procedures. The diagnosis of a cerebral EE, in all cases, was made by an experienced neurologist who was unaware of the echocardiographic findings. An EE was considered severe if it caused death or irreversible organ damage or if it needed specific medical or surgical treatment. Cutaneous manifestations were not included because their pathogenesis is mediated by several mechanisms. To detect silent embolism, a cerebral computed tomography (CT) scan and a thoraco-abdominal scan were performed within four days of hospital admission in 167 patients (95%). Computed tomography scans were performed with a contrast agent, except in five patients with severe renal failure. In these patients, abdominal echography was performed. Patients with moderate renal failure and/or an allergy to the contrast agent underwent contrast injection after adequate and specific preparation.

Statistical analysis. All analyses were performed using SPSS for Windows (SPSS Inc., Chicago, Illinois), release 9.0. Factors associated with embolism (univariate analysis) were determined using the chi-square test. The Fisher exact test (two-tailed) was used if the expected count in any cell was 5. The Student *t* test for unpaired data was used to compare age and length. An ascendant stepwise logistic regression was used to determine the independent risk factors for EE, with $p = 0.05$ to enter and $p = 0.10$ to remove. Data are expressed as the mean value ± SD. Statistical significance was established at $p < 0.05$.

Interobserver variability. Twenty randomly selected TEE studies, in double-blinded manner, were used to test interobserver variability for vegetation length and mobility, using the intraclass correlation for vegetation length and the kappa statistic for vegetation mobility.

RESULTS

Echocardiographic data. Echocardiography was positive for IE in 174 (98%) of the 178 patients, showing vegetations in 133 (75%), abscesses in 32 (18%), new periprosthetic regurgitation in 11 (6%) and aneurysm or valvular perforation in 15 (8%). Of 45 patients without a detectable vegetation, 29 had another major criterion (16 with abscesses, 6 with new periprosthetic regurgitations, 1 with a new valvular regurgitation and 6 with valvular perforations); 12 had only a minor echocardiographic criterion (valvular thickening or nonoscillating mass); and 4 had echocardiography that was not positive for IE. Of these four patients, three had BCs positive for typical microorganisms and at least three minor criteria (predisposing conditions, fever, vascular phenomena or immunologic phenomena); one patient had a very small vegetation found only during surgical inspection.

Embolic events. Of 178 patients, 66 (37%) had one or more EEs. The sites of embolization were the central nervous system (n = 27), lungs (n = 12), peripheral arteries (n = 9), spleen (n = 14), kidney (n = 8), eye (n = 1) and coronary artery (n = 1). Among the 66 EEs, 44 (67%) were considered severe (22 cerebral, 9 peripheral, 3 renal, 3 splenic, 5 pulmonary, 1 eye and 1 coronary). In 14 patients (8%), the diagnosis of EE was made exclusively with a CT scan.

There was no statistical difference between patients with and those without embolism in terms of age, gender, native or prosthetic valve, predisposing factors, the need for operation or death (Tables 2 and 3). Similarly, no significant difference was observed regarding the localization of vegetations (aortic or mitral) (Table 3). However, EEs were more frequent in patients with *Staphylococcal* IE (23 [53%] of 43 patients; $p = 0.023$; Table 1) and in patients with a vegetation on right-sided valves (9 [69%] of 13 patients; $p = 0.014$; Table 3). Furthermore, EEs were more frequent in 133 patients with echocardiographic vegetations than in 45 patients without them (43% vs. 20%, respectively; $p = 0.007$).

Influence of vegetation size. Vegetations were longer in patients with EEs than in patients without EEs (16 ± 7 vs.

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Table 3. Echocardiographic Localization of Vegetation and Risk of Embolism

	Total Group (n = 178)	Embolism Group (n = 66)	No Embolism Group (n = 112)	p Value*
Left native valve (total)	83 (46.6%)	30 (45.4%)	53 (47.3%)	0.80
Aortic	44 (24.7%)	14 (21.2%)	30 (26.7%)	0.4
Mitral	39 (21.9%)	16 (24.2%)	23 (20.5%)	0.56
Right valves	13 (7.3%)	9 (13.6%)	4 (3.6%)	0.014
Multiple valves	11 (6.2%)	7 (10.6%)	4 (3.6%)	0.103
Prosthetic valve (total)	22 (12.4%)	8 (12.1%)	14 (12.5%)	0.94
Aortic	11 (6.2%)	3 (4.5%)	8 (7.1%)	0.47
Mitral	11 (6.2%)	5 (7.6%)	6 (5.3%)	0.54
Pacemaker	4 (2.2%)	3 (4.5%)	1 (0.9%)	0.14
No vegetation	45 (25.3%)	9 (13.6%)	36 (32.1%)	0.0046

*Comparison between patients with embolic events and patients without embolism. Data are presented as number (%) of patients.

10 ± 6 mm; $p < 0.0001$). Embolic events occurred more frequently in patients with vegetation length >10 mm than in those with vegetation length ≤10 mm (60% vs. 23%, respectively; $p = 0.001$) (Fig. 1). Embolic events were particularly frequent in patients with very large vegetations: 30 EEs (70%) occurred in 43 patients with vegetation length >15 mm, whereas only 36 EEs (27%) occurred among 135 patients with a vegetation length ≤15 mm ($p = 0.001$).

Influence of vegetation mobility. Of 73 patients with moderately or severely mobile vegetations, 45 (62%) had EEs; of 105 patients with no or low mobile vegetations, only 21 (20%) had EEs ($p < 0.001$) (Fig. 1). Embolic events were particularly frequent among 30 patients (25 EEs [83%]) with both severely mobile and large vegetations (>15 mm), compared with all other patients with vegetations ($p < 0.001$).

Embolic events during therapy. Embolic events were infrequent during antibiotic therapy. Only 16 of 66 EEs occurred after initiation of specific treatment, three of which were silent embolisms detected by a CT scan. In these 16 patients, the size of the vegetation was frequently large (>10 mm in 13 patients [81%] and >15 mm in 9 patients [56%]). Moderate to severe vegetation mobility was observed in 13 (81%) of these 16 patients.

Silent embolism. Of 66 patients with EEs, 14 (21%) had EEs exclusively detected by a cerebral or thoraco-abdominal CT scan. Of these, 11 patients (78%) presented with a vegetation >10 mm in length; 2 had a vegetation <10 mm; and 1 had no vegetation. The vegetations showed important mobility in eight patients (57%); moderate in three; low in two; and absent in one. A significant relationship between EE and vegetation length and mobility persisted, even if we

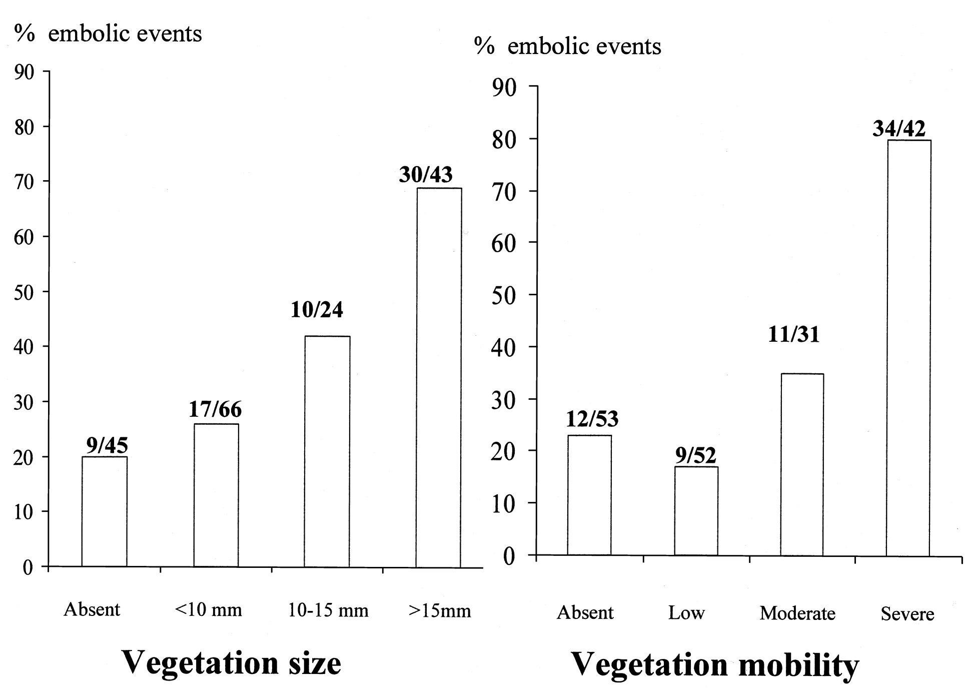

Figure 1. The incidence of EEs and their relationship with vegetation size and mobility. The numbers above the bars refer to the absolute number of patients with EEs relative to the total in the subgroup. EE = embolic events.

Table 4. Results of Univariate and Multiple Stepwise Logistic Regression Analyses

	Univariate p Value	Multivariate Analysis			
		p Value	β	Exp β	95% CI
Presence of vegetation	0.007	NS			
Vegetation length	< 0.0001	0.03	0.06	1.07	1.01–1.13
Vegetation mobility	< 0.001	0.0011	2.05	0.37	2.28–26.57
Mitral valve vegetation	NS	NS			
Aortic valve vegetation	NS	NS			
Right valve vegetation	0.014	NS			
Multiple valve vegetation	NS	NS			
Staphylococcal IE	0.023	NS			

CI = confidence interval; IE = infective endocarditis; NS = not significant.

excluded from the analysis the patients with a silent embolism ($p < 0.001$ and $p < 0.001$, respectively).

Logistic regression analysis. To determine which factors are important predictors of EEs, an ascendant stepwise logistic regression analysis was performed. The presence of vegetations, vegetation length and mobility, patient age and gender, vegetation site (mitral, aortic, right-sided valve and prosthetic or native valve) and the underlying organism, as identified by BCs, were entered as potential variables. The only significant risk factors for EEs were vegetation length ($p = 0.03$) and important mobility ($p = 0.001$) (Table 4). In contrast, low mobility ($p = 0.04$) and a negative BC ($p = 0.01$) were significantly associated with a low risk of EE.

Interobserver variability. Both echocardiographers agreed that a vegetation was present in 133 patients and absent in 45 patients; there was complete agreement on the site of involvement. Interobserver variability was very good for evaluation of vegetation length (kappa = 0.797), but worse for vegetation mobility (kappa = 0.714).

DISCUSSION

To the best of our knowledge, our study is the largest published series assessing the value of TEE in predicting EEs in a group of patients with definite IE according to the Duke criteria, and including silent embolism detected by a CT scan. The main result was that the risk of EEs was highly related to vegetation size and mobility, but not to other known risk factors for embolism in IE.

Embolic events in IE. The rate of systemic embolization in IE is estimated to be between 10% and 50% (1,12,17,22), but the exact incidence is difficult to define with certainty. Our incidence of 37% is between the range of other studies (1,12,17,22), but our results are probably overestimated because of the nearly systematic use of CT scanning in our patients, allowing the detection of 14 cases of purely silent embolism. In contrast, early operation is frequently performed in our center in cases of severe valvular destruction; 69 patients (63% of surgically treated patients) had an operation during the first 10 days after the diagnosis of IE, and this approach has probably prevented a number of clinical EEs (12,14). Early operation probably explains why only 16 of 66 EEs occurred after the antibiotic treatment was initiated. For the entire study group, new EEs occurred in 16 (9%) of 178 patients in our series, whereas the incidence was 13% in the series of Steckelberg et al. (1), who did not include silent embolism; 21.2% in the series of Rohmann et al. (15); and up to 44% in the recent series of De Castro et al. (12).

Embolic events and vegetation characteristics: report of previous studies. The main result of our study is that there was a strong relationship between vegetation characteristics and risk of EEs. It is not surprising that the incidence of EEs is higher in patients with large and mobile vegetations (13–15). Mugge et al. (14), in a prospective study of 105 patients with IE, found that patients with valvular vegetations >10 mm, as determined by TTE and TEE, had a higher frequency of EEs, as compared with those with vegetations ≤10 mm, even after the exclusion of patients with previous EEs. However, this difference was no longer present when IE was confined to an aortic or prosthetic valve (14). Sanfilippo et al. (13), in a retrospective analysis of 204 patients examined by TTE, used a composite score based on vegetation mobility, size, extent and consistency. They found, on multivariate analysis, that all of these vegetation features were associated with an increased risk of emboli. Similarly, in a prospective study of 118 patients with IE who underwent TEE, Rohmann et al. (15) found, on multivariate analysis, that risk factors for EEs were vegetation size >10 mm and mitral valve involvement.

However, other studies have failed to detect this relationship (1,3,12,16,17). Lutas et al. (3) and Steckelberg et al. (1) found no relationship between vegetation size and incidence of EEs. However, both studies included patients who already had EEs before the echocardiographic study. More importantly, both studies were performed using only TTE. For example, in the series of Steckelberg et al. (1), the vegetations were visualized in only 79 (38%) of 207 patients with IE. The use of TEE now allows a much higher sensitivity for the detection of vegetations; the determination of the size of the vegetation is probably less precise by TTE (9–11). So, the results of studies using only TTE may be interpreted with caution. More recently, Heinle et al.

Table 5. Results of Previous Studies

Author (ref.)	Relation Between EEs and Vegetation Size	Patients (n)	Embolic Events (%)	Echocardiography	Detected Vegetations (%)	Embolic Events During Therapy (%)
Lutas et al. (3)	Negative	77	22	TTE	56	ND
Mugge et al. (14)	Positive	105	31	TTE TEE biplane	91	19
Jaffe et al. (16)	Negative	70	43	TTE	78	16
Sanfilippo et al. (13)	Positive	204	33	TTE	75	ND
Steckelberg et al. (1)	Negative	207*	13	TTE	38	13
Rohmann et al. (15)	Positive	118	26	TEE	42	21
Heinle et al. (17)	Negative	41	49	TTE	73	49
Werner et al. (23)	Positive, >20 mm	106	35	TEE TEE monoplane (28%)	92	ND
De Castro et al. (12)	Negative	57†	44	TTE TEE multiplane	80	44
Present study	Positive	176	37	TEE multiplane	75	9

*Only with left-sided native valve infective endocarditis (IE). †Only with native valve IE.
EEs = embolic events; ND = not defined; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

(17), using TTE, and De Castro et al. (12), using TEE, also failed to demonstrate any relationship between EE and echocardiographic characteristics; unfortunately, in both studies, silent embolisms were not included in the analysis and the number of patients studied was small. As shown in Table 5, all the studies with >100 patients found a significant relationship between EE and vegetation size, except for Steckelberg et al. (1).

Therefore, the reasons for the conflicting results between series include poor standardization of diagnostic criteria for IE, detection of silent embolism (or not), suboptimal image quality obtained with TTE in older series and a small sample size (Table 5).

Results of the present study. Our study overcomes all of these limitations; a large number of patients (n = 178) with strict criteria for IE were studied. All echocardiographic studies were performed using multiplane TEE, allowing an improved morphologic characterization of vegetations (9–11). Moreover, this is the first study in which CT scanning was performed in 95% of patients to detect silent embolism, in order to minimize the risk of underestimation of the true incidence of EE. Finally, early operation was performed in a large number of patients, and we believe that the incidence of EEs in our series represents the true incidence of EEs in the era of early operation.

Our study clearly showed a significant relationship between the presence of echocardiographically documented vegetations and the occurrence of EEs (43% of EEs in patients with vegetations vs. 20% of EEs in patients without vegetations, $p = 0.007$); between vegetation size and EEs (60% of EEs in patients with vegetation size >10 mm vs. 23% of EEs in patients with vegetations ≤10 mm, $p = 0.001$); and between vegetation mobility and EEs (62% of EEs in patients with mobile vegetations vs. 20% of EEs in patients without high mobility, $p < 0.001$). Embolic events were particularly frequent among 30 patients (25 EEs [83%]) with both severely mobile and large vegetations (>15 mm). These results emphasize the importance of both vegetation size and mobility in predicting subsequent EEs. This was confirmed by a multivariate analysis showing that mobility and size of the vegetation were the only predictors of EEs. On multivariate analysis, vegetation mobility was an even better predictor of EEs, as compared with vegetation size. However, we think that vegetation size is a better clinical predictor of EEs because of its lower interobserver variability.

Other risk factors for embolism. In our series, age, gender and mitral localization were not correlated with a significant risk of EEs. Mugge et al. (14) and Rohmann et al. (15) found a significant correlation between EEs and localization of vegetations on the mitral valve. A proposed explanation was that the large movement of the anterior mitral leaflet may destabilize attached vegetations (15). However, the number of EEs was relatively small in these series, and in our study as well as in others (1,12,13,23), such a relationship was not found and the percentage of EEs was similar between aortic and mitral IE.

In contrast, in agreement with previous studies (12,13) we found a high incidence of EEs in patients with vegetations on right-sided valves (9 [69%] of 13 patients). However, in our series, this tendency was not confirmed by multivariate analysis, probably because of the small number of patients with right-valve IE. Similarly, *Staphylococcal* infection was associated with a high incidence of EEs on univariate analysis. This finding is in agreement with previous reports (15,22) showing that *Staphylococcus aureus* is a particularly virulent pathogen. However, multivariate analysis failed to confirm this relationship, probably because the embolic potential of *Staphylococcal* infection is correlated with vegetation length and mobility (13). In contrast, negative BCs were significantly correlated with a lower risk of EEs.

Study limitations. This study has several limitations. First, although CT scanning was performed in almost all patients, the true incidence of silent EEs is unknown and may be underestimated. Second, embolization may reduce the size and mobility of the vegetation, and inclusion of patients with previous EEs may have resulted in underestimation of the relationship between vegetation size and risk of EEs (3,22). Third, the main limitation of the study is that 61% of the patients underwent surgery. It is possible that some patients with large and mobile vegetations underwent early operation before a potential EE. Consequently, the natural history of the emboli is potentially altered by the operation. Another limitation is the possible effect of antibiotic treatment on the incidence of embolism. In our series, EEs were infrequent during treatment, as only 11 [16%] of 66 EEs occurred after initiation of antibiotic treatment. However, a repeat CT scan was not systematically performed after treatment, so the exact incidence of new EEs may have been underestimated. Nevertheless, the objective of this study was not specifically to address the effect of medical treatment on the rate of embolism, but rather to test the utility of TEE to predict embolic risk. Similarly, the benefit of surgery in patients with large and mobile vegetations was not specifically addressed in this study. Although our results suggest a need for operation in patients with both large and mobile vegetations, we can only conclude, on the basis of our data, that these patients have a higher incidence of emboli. The real benefit of early operation to avoid an embolic event in these patients must be weighed against the risk of valve surgery in patients without congestive heart failure or uncontrolled infection. It may also be argued that the "clinical" risk of a vegetation depends on the potential site of embolization. For example, the consequences of a cerebral embolism may be much more serious than either a right-sided emboli or a splenic or renal emboli. Unfortunately, the severity of an EE cannot be predicted before this event occurs; for example, of 27 cases of cerebral embolisms, only 22 caused permanent organ damage. In contrast, although right-sided and splenic emboli are usually well-tolerated, splenic abscesses were noted in three patients in our series, one of whom needed emergency surgery, and pulmonary embolism from a right-sided vegetation caused acute respiratory failure in five patients. Finally, in our study we did not consider the echogenicity of the vegetation because of its high technical variability (12,13), depending on gain setting, distortion by lateral resolution or transducer selection, which hinder correct evaluation and comparison among different series.

Clinical implications. Our study clearly shows that the presence of vegetations on TEE is predictive of embolism, and that the morphologic characteristics of vegetations are helpful in predicting EEs in both mitral and aortic valve IE.

Patients with vegetations >10 mm and with mobile vegetations have an increased risk of EEs. Patients with a vegetation size >15 mm and with high mobility are at a very high risk of EEs. Our study also suggests that early operation may potentially reduce the incidence of EEs and may be recommended in these patients, irrespective of the degree of valve destruction, heart failure and response to antibiotic therapy. However, the study was only designed to test the utility of TEE to identify embolic risk, and further studies are needed to assess the possible benefits of early versus delayed operation, as well as of antibiotic treatment, on the rate of embolism in patients with IE.

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