Clin. Cardiol. 21, 572–578 (1998)

Relative Value of Clinical and Transesophageal Echocardiographic Variables for Risk Stratification in Patients with Infective Endocarditis

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Summary

Background: Infective endocarditis remains a life-threatening disease, and its optimal management is of paramount importance. Transesophageal echocardiography (TEE) is useful for the diagnosis of endocarditis-induced lesions, but the prognostic significance of the method remains controversial.

Hypothesis: The purpose of this study was to relate clinical and TEE characteristics to the occurrence of mortality and/or systemic embolization in a consecutive series of 45 patients with a diagnosis of infective endocarditis.

Methods: All patients underwent at least one monoplane TEE. Clinical data, episodes of embolization, and echocardiographic characteristics were prospectively recorded. Stepwise logistic discriminant analysis was performed to identify the independent variables that best predicted three binary outcomes: systemic embolization, death, and systemic embolization and/or death.

Results: Twelve of the 45 patients (27%) died from the endocarditis. Significant univariate predictors of death were the presence of paravalvular abscess ($p = 0.025$), number of vegetations ($p = 0.021$), *Staphylococcus aureus* isolated in blood cultures ($p = 0.002$), medical treatment alone ($p<0.002$), and systemic embolism ($p<0.001$). In multivariate analysis, systemic embolism ($\chi^2 = 29.3$; $p<0.01$), echocardiographic evidence of paravalvular abscess ($\chi^2 = 5.6$; $p = 0.018$), *Staphylococcus aureus* endocarditis ($\chi^2 = 5.5$; $p = 0.016$), and medical treatment alone ($\chi^2 = 5.11$; $p = 0.024$) emerged as optimal predictors of death. Systemic embolization occurred in 12 patients. Independent variables predicting systemic embolization were a total length of vegetations > 14 mm ($p = 0.01$), greater age ($p = 0.02$), and medical treatment alone ($p = 0.03$). When two or more vegetations were observed, the total length is the sum of the individual sizes. Independent risk factors for the development of systemic emboli and/or death as a combined end point were total length of vegetations on TEE ($\chi^2 = 6.4$; $p = 0.003$) and medical treatment alone ($\chi^2 = 4,1$; $p = 0.047$).

Conclusions: High-risk patients may be identified by the combination of clinical variables and TEE characteristics.

Key words: echocardiography, embolism, endocarditis, prognosis

Introduction

Infective endocarditis remains a life-threatening condition,[1] and its prompt diagnosis is essential for successful management. Echocardiography is a useful tool in the diagnosis of endocarditis-induced lesions, especially from the transesophageal window, because of its very high sensitivity and specificity.[2–4] Some studies have suggested a higher incidence of complications among patients with vegetations demonstrated by echocardiography, or in patients with larger vegetations.[5–7] In contrast, in other studies, the presence or size of echocardiographically detected vegetations did not predict systemic embolization, need for surgery, or death.[8–9] In addition, it has been suggested that the relative risk of embolic events is microorganism dependent and declines rapidly during the time course of antibiotic therapy.[9] However, most investigators have defined echocardiographic vegetation characteristics from the transthoracic approach, and few studies have assessed the relative contribution of clinical and echocardiographic variables for risk stratification. Thus, although the usefulness of transesophageal echocardiography (TEE) for the

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Received: January 8, 1998
Accepted with revision: May 21, 1998

diagnosis and assessment of endocarditis is well demonstrated, the prognostic implications of the method remain controversial. The aims of this study were (1) to determine the usefulness of TEE in the prediction of complications in patients with endocarditis, and (2) to assess whether TEE improves the prognostic value of clinical parameters.

Methods

Patients

Forty-five patients with infective endocarditis according to the Duke's criteria were studied at our department by monoplane TEE between the introduction of monoplane TEE and the availability of multiplane probe.[10] There were 30 men and 15 women, ranging in age from 30 to 82 years with a mean of 58 ± 16 years. Eleven patients (24%) were referred with prosthetic valve endocarditis and 16 (36%) had preexisting cardiac disease. All patients gave informed consent for a TEE examination. Histopathologic evidence of endocarditis was obtained in 26 patients (58%) after surgery in 19, and by autopsy in 7.

Clinical Data

Patients underwent a detailed physical examination, and the following variables were recorded: age, gender, antibiotic treatment before admission, past history of heart disease, clinical evaluation of heart failure on hospital admission according to the New York Heart Association (NYHA) classification, and the occurrence of the following in-hospital complications: congestive heart failure, need for surgery, or embolic events. After hospital discharge, the patients were followed up for 5 months by outpatient visits or by telephone contact with their general physician.

Assessment of Embolization

Episodes of embolization (pulmonary or systemic arterial embolism) were recorded by a clinician who was unaware of echocardiographic data. The diagnosis of cerebral embolism was based on a sudden appearance of neurologic disorders (transient ischemic attack in five patients, stroke in three, and both in two patients). Pulmonary embolism was suspected in two patients with right-sided endocarditis and the diagnosis was confirmed by radiographic and scintigraphic manifestations. Peripheral systemic embolism was defined as sudden occlusion of a major artery and was diagnosed by clinical and radiographic examination. Microvascular embolic episodes limited to skin were not included.

Echocardiographic Evaluation

Transesophageal echocardiographic examination was performed in all patients within 1 week of hospital admission, and was repeated during the hospital course and after discharge when necessary. No complications were encountered during examinations. All echocardiograms were reviewed by two independent observers blinded to clinical data. The echocardiographic characteristics noted at the first TEE study were included in the analysis. The diagnosis of a vegetation was made if an abnormal echogenic mass attached to a leaflet surface or the subvalvular apparatus was seen continuously throughout the cardiac cycle. Echocardiographically detected vegetations were classified according to their number, size, mobility, consistency, extension, and site of involvement. Size was measured by maximal width and length. In the presence of more than one vegetation, the total length was obtained by the sum of the individual lengths (Fig. 1). Mobility, extent and consistency were graded on a scale of 1 to 4.[11] The mobility score was Grade 1, fixed vegetation with no independent motion; Grade 2, fixed base but mobile free edge; Grade 3, pedunculated vegetation; and Grade 4, prolapsing vegetation, crossing the coaptation point of the leaflet at some time during the cardiac cycle. The extent of a vegetation was scored as Grade 1, single vegetation; Grade 2, multiple vegetations, limited to a single valve leaflet; Grade 3, involvement of multiple leaflets; and Grade 4, involvement of extravalvular structures. The score for the consistency of a vegetation was Grade 1, completely calcified vegetation; Grade 2, partially calcified vegetation; Grade 3, denser than myocardial structures, not calcified; and Grade 4, density equal or below myocardial echoes. The echocardiographic score developed by Sanfilippo *et al.*[12] was calculated. Perivalvular abscess was defined as an abnormal echolucent area in the paravalvular tissue.[13] Valvular regurgitation was assessed by pulsed and continuous wave Doppler and color flow mapping. The severity of valvular regurgitation was obtained by standard criteria[14, 15] and classified as trivial, mild, moderate, or severe.

Statistical Analysis

Mean values and standard deviations were computed for all quantitative parameters, and proportions were computed for binary or discrete variables. Three binary outcome variables

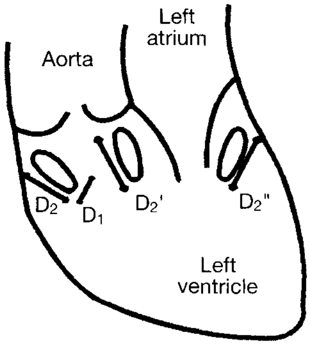

FIG. 1 Vegetation size was measured from stop frame images obtained by monoplane transesophageal echocardiography; maximum width (D1) and length (D2) were noted. When > 1 vegetation was observed, the total length was recorded as the sum of the lengths of the individual vegetations. D3 = D2 + D2' + D2".

were analyzed separately (systemic embolization vs. no embolic event, survivors vs. nonsurvivors, systemic embolization and/or death vs. others). For these three outcomes, data were first examined by univariate analysis for differences between subgroups. Quantitative variables were tested by *t*-test and nominal findings by a chi-square test. Results were considered significant at the 5% critical level. Stepwise logistic discriminant analysis was used to identify the independent variables that best predicted outcome.

Results

Clinical Variables and Outcome

The selection of antimicrobial therapy was based on clinical presentation. In unstable patients with acute endocarditis, empiric antimicrobial therapy (vancomycin and an aminoglycoside) was initially used after obtaining four blood cultures at hourly intervals. When the causal organism was identified, the antibiotics were adjusted according to Sanford *et al.*[16] Blood cultures identified the causative microorganism in 30 of 45 patients: 14 were infected by *Staphylococcus aureus*, 7 by *Streptococcus viridans*, 5 by *Staphylococcus epidermidis*, 3 by *Streptococcus fecalis*, and 1 had mycotic endocarditis. Among patients with culture-negative endocarditis, eight had received antibiotic agents before admission. Of 45 patients, 23 (51%) had heart failure defined as NYHA class 2 to 4. Elective valve replacement was performed in 19 of 45 patients (42%). The mean interval between hospital admission and surgical intervention was 12 days. In seven patients, noncardiac surgery was necessary. The indications for noncardiac surgery were cerebral hemorrhagic infarct drainage in two patients, cerebral mycotic aneurysm repair in one, Fogarty intervention for a peripheral embolic event in two, nephrectomy in one, and drainage of the pericardium in one patient. Nine patients died during the hospital phase, one early after cardiac surgery, one in the perioperative period as a result of cerebral bleeding, one 12 days after intervention of cerebral mycotic aneurysm repair, and the other six during antimicrobial therapy. During the follow-up period (5 ± 2 months), three patients died of a cardiac cause: one suddenly, one from rupture of perivalvular abscess, and one in acute heart failure secondary to ventricular septal rupture.

Embolic Events

Pulmonary emboli were diagnosed in two patients with tricuspid endocarditis. Systemic embolic events were noted in 12 of the 45 patients (27%). Cerebral embolization was the most frequently observed embolic event, occurring in 10 patients (22%). Peripheral emboli were recorded in five patients, three of whom had multiple embolic events.

Echocardiographic Findings

Valvular involvement was left-sided in 41 patients and right-sided in 4. Twenty-two of 45 patients had aortic valve endocarditis. Mitral vegetations were found in 16 patients, and both aortic and mitral valves were involved in 3. Tricuspid endocarditis was diagnosed in four cases. In all 45 patients, at least one vegetation was observed by the two independent observers. Characteristics of vegetations are presented in Table I. Valvular regurgitation was trivial in 10 patients, mild in 17, moderate in 11, and severe in 7. One patient had a massive vegetation on the ventricular site of a bioprosthetic aortic valve, causing severe outflow tract obstruction and low cardiac output. Seven patients had annular and/or myocardial abscesses; three of these patients developed atrioventricular block.

Predictors of Systemic Embolic Events

A comparison was made between the 12 patients with a systemic embolic event and the 33 patients without embolization (Table II). There were no significant differences in gender, incidence of previous valvular disease or prosthetic valve involvement, site of affected valves, presence of abscess, and the following vegetation characteristics: mobility, extension, consistency, and Sanfilippo score.[12] Patients who presented an embolic event were older (61 ± 3 vs. 51 ± 4, $p = 0.03$) and *S. aureus* was often isolated in blood cultures (9/12 vs. 5/33, $p = 0.002$). With TEE, the number of vegetations (5/12 vs. 7/33; $p = 0.02$), the maximum vegetation length (15 ± 2 vs. 10 ± 1, $p = 0.04$), and total length (18 ± 8 vs. 11 ± 5, $p = 0.01$) were higher in patients who had suffered systemic embolization.

TABLE I Echocardiographic characteristics of vegetations

Variables	No. of patients (%)
Number	
1	27 (59)
2	11 (25)
3	7 (16)
Length	12 ± 7 mm
Width	6 ± 3 mm
Total length	15 ± 6 mm
Mobility	
1	13 (29)
2	12 (26)
3	11 (24)
4	9 (21)
Extension	
1	28 (62)
2	5 (10)
3	3 (7)
4	9 (21)
Consistency	
1	9 (19)
2	21 (46)
3	10 (23)
4	5 (12)
Sanfilippo score (10)	6.1 ± 1.9

TABLE II Comparison between patients with or without embolic events

Variables	Emboli n = 12	No emboli n = 33	p Value
Clinical			
Age (years)	61 ± 3	51 ± 4	0.03
Sex (% women)	25	36	NS
Staph. aureus (%)	9 (75)	5 (16)	0.002
Previous valvular disease (%)	5 (41)	11 (33)	NS
Prosthetic valve (%)	3 (25)	8 (24)	NS
Aortic valve (%)	9 (75)	16 (48)	NS
Mitral valve (%)	6 (50)	13 (40)	NS
Surgery (%)	3 (25)	16 (48)	NS
TEE			
> 1 V (%)	5 (42)	7 (21)	0.02
Width (mm)	6 ± 1	5 ± 1	NS
Length (mm)	15 ± 2	10 ± 1	0.04
Total length (mm)	18 ± 8	11 ± 5	0.01
V mobility score > 1 (%)	11 (92)	21 (64)	NS
V extension score > 1 (%)	5 (58)	12 (36)	NS
V consistency score > 1 (%)	11 (92)	27 (82)	NS
Sanfilippo score	6.9 ± 1.5	5.8 ± 2.1	NS

Abbreviations: Staph. = staphylococcus, V = vegetation, TEE = transesophageal echocardiography, NS = not significant.

Three independent variables predictive of systemic embolization were selected stepwise from the multivariate analysis: total length of vegetations on TEE ($\chi^2 = 6.9$; $p = 0.01$), greater age ($\chi^2 = 6.2$; $p = 0.02$), and medical treatment alone ($\chi^2 = 5.3$; $p = 0.03$). The best cut-off value of total length of vegetations for distinguishing high and low risk of embolism was 14 mm. A total length of vegetations > 14 mm accurately predicted clinically detected embolization: sensitivity 71%, specificity 93%, positive predictive value 83%, negative predictive value 88%, and accuracy 87%.

Distinction between Survival and Death

Table III presents the comparison of clinical and echocardiographic findings between survivors and nonsurvivors. There were no significant differences in age, gender, previous valvular disease, congestive heart failure, site and number of affected valves, grade of valvular regurgitation or vegetation size, mobility, extension, consistency, and Sanfilippo score. In univariate analysis, systemic embolic event (6/12 vs. 6/33, $p < 0.001$), medical treatment alone (11/12 vs. 16/33, $p < 0.002$), *S. aureus* isolated in blood cultures (8/12 vs. 6/33, $p = 0.002$), TEE evidence of perivalvular abscess (5/12 vs. 2/33, $p = 0.0025$) and the number of vegetations (6/12 vs. 6/33, $p = 0.021$) were found to be predictors of death. With multivariate analysis, the occurrence of systemic emboli during the hospital course was the most predictive parameter for selecting high-risk patients ($\chi^2 = 29.3$; $p < 0.01$). Perivalvular abscess ($\chi^2 = 5.6$; $p = 0.018$), *S. aureus* endocarditis ($\chi^2 = 5.5$; $p = 0.016$) and medical treatment alone ($\chi^2 = 5.11$; $p = 0.024$) significantly improved the predictive ability of an embolic episode. When death and systemic embolization were combined as an end point, two independent variables were selected stepwise from multivariate analysis: the total length of vegetations on TEE ($\chi^2 = 6.4$; $p = 0.003$) and medical treatment alone ($\chi^2 = 4.1$; $p < 0.05$).

Discussion

Risk Stratification in Infective Endocarditis

The two major complications of infective endocarditis are systemic embolism and death. Embolization may result in major sequelae. Because full anticoagulation is required during open heart intervention, devastating stroke due to cerebral emboli usually precludes early surgery. The proper indication for surgery and its optimal timing are crucial in the therapeutic management. This issue remains controversial. Some groups recommend immediate surgery as soon as significant complications occur;[17, 18] others recommend delaying surgery and monitoring the patients.[19–21]

The echocardiographic detection of vegetation is useful for the diagnosis of active infective endocarditis[4, 22] and is now included in the Duke's criteria for defining the likelihood of having the disease.[10] The advent of the transesophageal window has further improved the diagnostic accuracy of the technique. However, controversy persists on the prog-

TABLE III Comparison between survivors and nonsurvivors

Variables	Death n = 12	Survival n = 33	p Value
Clinical			
Age (years)	60 ± 8	64 ± 10	NS
Sex (% women)	18	39	NS
Staph. aureus (%)	8 (67)	6 (18)	0.002
Previous valvular disease (%)	2 (17)	14 (42)	NS
Prosthetic valve (%)	2 (17)	9 (27)	NS
Aortic valve (%)	8 (67)	17 (52)	NS
Mitral valve (%)	5 (42)	14 (42)	NS
Heart failure (%)	9 (75)	14 (42)	NS
Systemic emboli (%)	6 (50)	6 (18)	<0.001
Medical treatment alone (%)	11 (92)	16 (48)	<0.002
TEE			
Abscess (%)	5 (42)	2 (6)	0.0025
> 1 V (%)	6 (50)	6 (18)	0.021
Width (mm)	6 ± 1	5 ± 1	NS
Length (mm)	15 ± 7	11 ± 6	NS
V mobility score > 1 (%)	10 (83)	22 (67)	NS
V extension score > 1 (%)	6 (50)	11 (33)	NS
V consistency score > 1 (%)	9 (75)	27 (81)	NS
Sanfilippo score	6 ± 1	6 ± 2	NS

Abbreviations as in Table II.

nostic role of cardiovascular ultrasound.[23] Whereas some studies have suggested that transthoracic detection of a vegetation carries increased risk of embolization, congestive heart failure, or death,[5,6] other investigators found no relation between the presence of vegetations and the frequency of complications.[8,9] Subsequent works showed a relation between vegetation size and the risk of embolization,[7,12,24] whereas others have found no such association.[12] Furthermore, few studies[7,13] have assessed the independent prognostic role of clinical and echocardiographic parameters.

The major findings of this study are twofold: (1) clinical and TEE variables provide complementary information for predicting the outcome of patients with infective endocarditis, and (2) the sets of independent variables differ for the prediction of the two major complications, systemic embolism and death.

Prediction of Embolic Events

Six univariate predictors of systemic embolism were identified in this study: greater age, *S. aureus* endocarditis, two or more vegetations, the maximum length of a vegetation, the total length of vegetation lesions, and medical therapy alone. With stepwise logistic multivariate analysis, three parameters were found to be independently associated with systemic embolization: the total length of vegetation lesions, a greater age, and the absence of elective valve replacement.

The patient's age was also an important predictor of embolization in the study by Sanfilippo *et al.*[12] In contrast, Werner *et al.* observed a higher incidence of major embolism in younger patients.[25] In other studies, age was not entered as independent variable in a multivariate analysis. Microorganism dependence of embolic risk is unclear. Steckelberg *et al.*,[9] in a series of 207 patients, reported that the embolic rate was sevenfold higher in viridans streptococcal endocarditis compared with *S. aureus* infection. In the study by Jaffe *et al.*,[24] the patients at highest risk for embolization were those with *Haemophilus influenzae* endocarditic lesions. In *S. aureus* endocarditis, embolization was found to occur early, to be multiple, to involve the central nervous system, and to carry a worse prognosis.[26] In the present study, *S. aureus* lesions were frequently associated with emboli (75 vs. 16%) but the microorganism was not selected as an independent variable in the multivariate analysis, probably because it strongly correlated with vegetation size. The discrepancies between reports on the influence of the infective organisms may be explained by differing proportions of causal bacteria. For instance, *Haemophilus influenzae* was not found to be a causal agent in any of our patients.

The total length of the vegetation material was selected as the best predictor of embolic events. When stepwise logistic analysis was repeated without this rarely used parameter, the presence of > 1 vegetation emerged as an independent variable. Although a close relationship between vegetation size and embolic risk makes sense, published data are conflicting. Most investigators have used a cut-off value of 10 mm for distinguishing large from smaller lesions. Using TEE, Mügge *et al.* found that patients with a vegetation > 10 mm had a significantly higher incidence of embolic events than those with a vegetation < 10 mm.[7] In our studies, the best cut-off value of total length of vegetations was 14 mm. However, monoplane TEE may lead to an underestimation of lesion length and some small vegetations may be missed.[11] The cut-off value would thus probably have been different—higher—if multiplane imaging had been performed.

Absence of surgical intervention was found to be associated with systemic embolism. When the central nervous system is the site of embolization, with the occurrence of devastating stroke, there is a tendency to delay surgery by 2 to 4 weeks to avoid neurologic worsening associated with anticoagulation.[27] This strategy is, however, challenged by a preliminary report[28] indicating that urgent surgical intervention after a first cerebral thromboembolic event significantly improves the prognosis, while later interventions are associated with an increased incidence of hemorrhagic complications.

Mobility was not found to be associated with a higher incidence of systemic embolization in this study. Mobility was a discrete variable and was thus less likely to be a significant parameter; interobserver variability has been found to be higher for this characteristic than with regard to size.[29]

Prediction of Mortality

Systemic embolization was the most predictive variable associated with mortality. Three other independent parameters were selected stepwise by the multivariate analysis: a paravalvular abscess demonstrated by TEE, *S. aureus* endocarditis, and medical therapy alone.

Major embolization has been repeatedly found to carry a high mortality rate,[30,31] mainly when the central nervous system is involved, which was the case in the majority (10/13) of our patients who suffered this complication.

The detection of abscesses suggests more extensive destruction of the valve structure and is associated with a higher mortality rate.[14,32] Surgery usually is considered mandatory when an abscess is demonstrated, but surgical techniques are more delicate, and proper timing of the intervention may be difficult. Well-delineated, echo-free perivalvular cavities with intracavitary color Doppler signals appear to be pseudoaneurysms, without residual pus[33] and, theoretically, surgery could be easier at that stage.

S. aureus was the most common infecting organism; this may be related to the setting of a tertiary teaching hospital.[34] Staphylococcal infective endocarditis has been found to have a higher mortality than that of streptococcal endocarditis,[30,35] especially in the presence of systemic embolic complications.[36] In this series, *S. aureus* was indeed selected as a risk factor for mortality, independent of embolization.

Caution is required in interpreting the absence of surgery as a parameter associated with an adverse event. Early surgery seems to have a favorable influence on prognosis, especially when successful antibiotic therapy precedes valve replacement.[37] However, the occurrence of serious complications preceding death, such as a stroke syndrome, may have represented a treatment bias by the attending physicians, probably influenced by fear of hemorrhagic complications inducible by surgery.

Conclusions

Our results indicate that TEE improved the prognostic value of clinical variables. A recent investigation suggested that transthoracic echocardiography should be the diagnostic procedure of choice and that TEE should be reserved only for patients who have prosthetic valves and in whom transthoracic echocardiography is either technically inadequate or indicates an intermediate probability of endocarditis.[38] Transesophageal echocardiography imaging is, however, superior for estimating the maximal length of vegetations and for diagnosing the presence of an abscess. In a recent study, echocardiographic vegetation characteristics as assessed by the transthoracic window were not helpful in predicting the risk of embolic complications.[29] As TEE was not always preceded by transthoracic echocardiography in our population, it was not possible to determine the incremental prognostic value of the transesophageal window. The findings of this study suggest, however, that TEE could be superior to transthoracic echocardiography for the assessment of prognosis in this severe disease.

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