Prognostic significance of vegetations detected by two-dimensional echocardiography in infective endocarditis

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The identification of a vegetation is a hallmark manifestation of infective endocarditis. Although initially described by Osler[1] precisely 100 years ago, in his Gulstonian lectures on malignant endocarditis, the antemortem recognition of vegetations has only recently been made possible by echocardiography. Several reports have emphasized the clinical utility of both M-mode[2-5] and two-dimensional echocardiography (2DE)[5-8] in detecting vegetations and confirming the clinical diagnosis of infective endocarditis. More recent reports have suggested that the echocardiographic visualization of a vegetation may additionally stratify a patient into a high-risk subgroup warranting more aggressive management.[3, 9-13]

This report reviews our recent experience with vegetations detected by 2DE in patients with clinically diagnosed infective endocarditis. We specifically sought to identify the prevalence and characteristics of 2DE-detected vegetations in patients with infective endocarditis and to determine whether these 2DE-detected vegetations identified a high-risk subgroup.

METHODOLOGY

Patient population. Over a 54-month interval, 74 patients with clinically diagnosed infective endocarditis were seen at the University of Michigan Medical Center. The clinical diagnosis of infective endocarditis was based on a standard clinical definition with specific criteria[14]: the presence of a heart murmur with at least two positive blood cultures obtained at separate times yielding the same organism and at least one of the following: (1) a new or changed heart murmur, (2) peripheral stigmata of endocarditis (e.g., embolic phenomena or splenomegaly), or (3) laboratory evidence of endocarditis (e.g., positive rheumatoid factor, myoglobulins, or "active" urinary sediment). All but two of our patients met these specific clinical criteria. Two patients with culture-negative endocarditis in the setting of previous antibiotic administration were included because of overwhelming clinical evidence of infective endocarditis meeting all of the other clinical criteria. A total of 24 patients were excluded from the study, including 17 patients who had not received echocardiographic evaluation, five patients with prosthetic valve endocarditis, and two patients with incomplete data.

Echocardiographic technique. 2DE was performed with a phased-array 2DE sector scanner and a 2.25 MHz transducer. Standard cross-sectional images of the heart were obtained in multiple planes[15] and stored on videotape for later playback analysis. The diagnosis of vegetation was made only if a discrete echogenic mass was visualized, which was mobile and attached to the valve structure (Figs. 1 and 2). Vegetations were not diagnosed if the valve was symmetrically thickened or immobile in the setting of a previous history of valve disease. In those patients with a vegetation, the size of the vegetation was measured by electronic planimetry of the largest two-dimensional area visualized on multiple views.

All patients were treated medically according to clinical and laboratory data. Patients were evaluated for the presence or absence of major arterial embolic complications, new-onset congestive heart failure, necessity for surgical intervention, and clinical outcome. All data are expressed as mean ± standard error of the mean.

OBSERVATIONS

A total of 50 patients with clinically diagnosed infective endocarditis were identified. There were 29 men and 21 women with a mean age of 41 years

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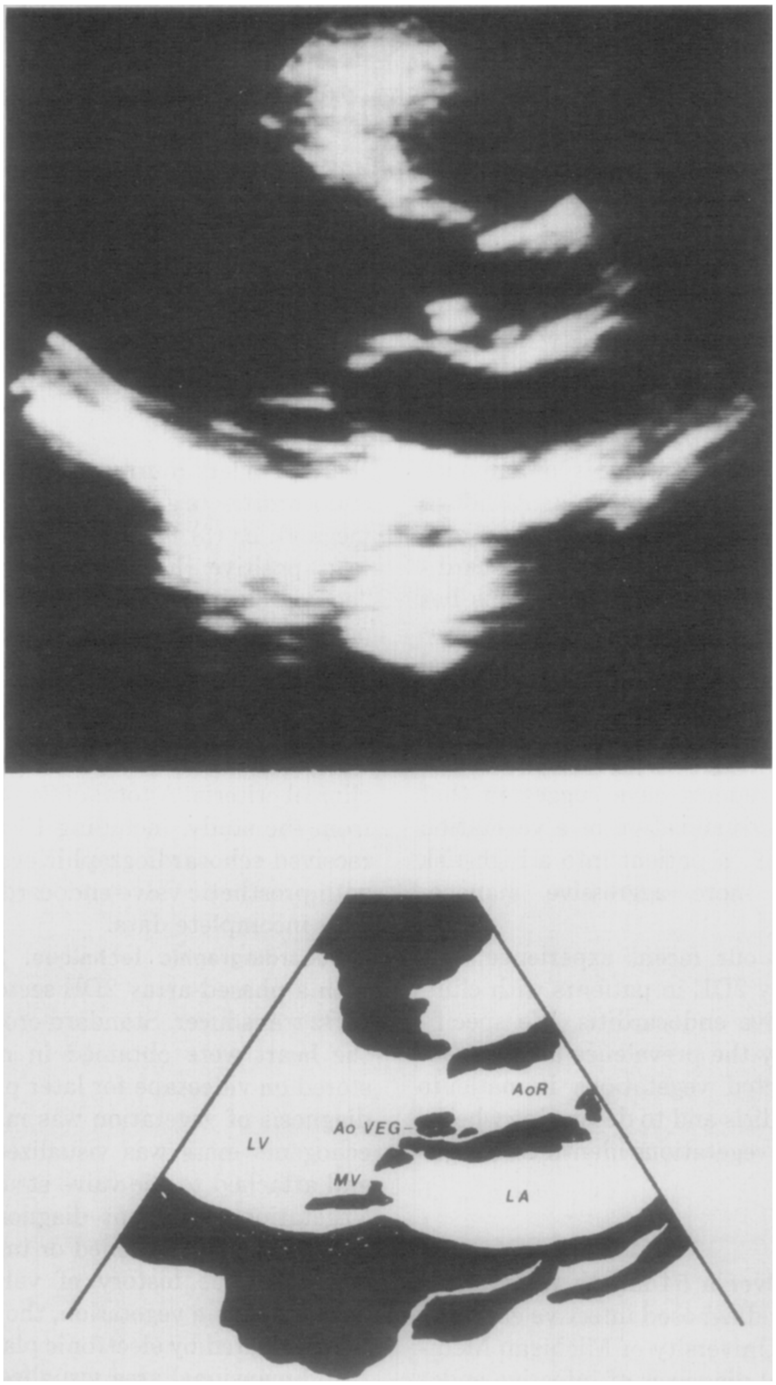

Fig. 1. *Top,* Two-dimensional echocardiographic long-axis view in a patient with aortic valve vegetation. *Bottom,* Schematic representation of 2DE view. *AoR* = aortic root; *Ao VEG* = aortic valve vegetation; *LA* = left atrium; *LV* = left ventricle; *MV* = mitral valve.

(range 19 to 76 years). Predisposing factors included intravenous drug abuse in 19 (38%), previous rheumatic disease in six (12%), degenerative valvular disease in five (10%), and mitral valve prolapse in five (10%). The infective organisms are summarized in Table I. Staphylococcus and streptococcus strains were the most common bacteria, responsible for 82% of all cases.

2DE identified a definite vegetation in 21 (42%) patients. The site of vegetation was the aortic valve in 10, the mitral valve in eight, and the tricuspid valve in three. The mean size of the vegetation was

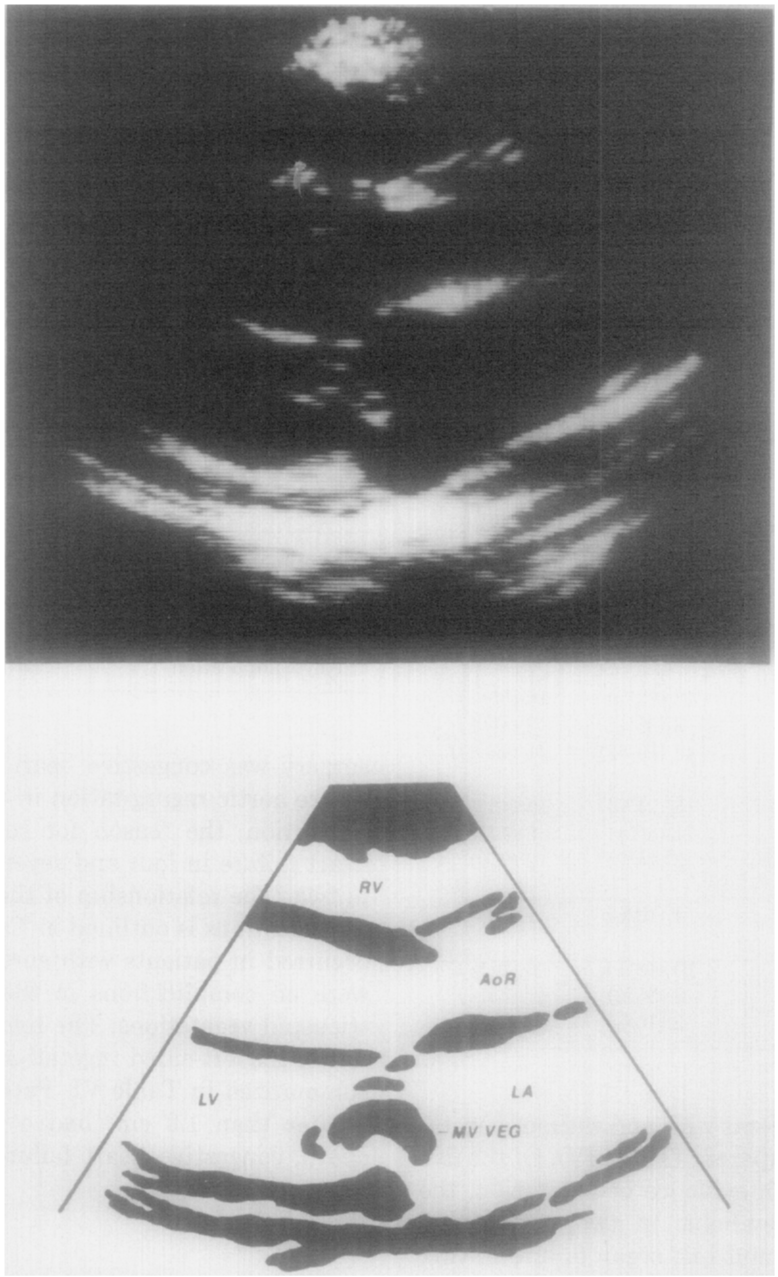

Fig. 2. *Top,* Two-dimensional echocardiographic long-axis view in a patient with mitral valve vegetation. *Bottom,* Schematic outline. *AoR* = aortic root; *LA* = left atrium; *LV* = left ventricle; *RV* = right ventricle; *MV veg* = mitral valve vegetation.

1.2 cm^2 (range 0.2 to 2.7 cm^2). Specific clinical characteristics of the two subgroups are summarized in Table II. Patients with vegetation were similar to those without vegetation with respect to sex distribution and age. Most patients with a history of intravenous drug abuse did not have vegetations, and this was associated with a higher frequency of staphylococcus bacteria in those patients without 2DE-detected vegetations.

Specific complications are summarized in Table III. A total of 49 life-threatening complications occurred; 18 (86%) of 21 patients with vegetations had one or more complications, whereas 18 (62%) of 29 patients without vegetations had complications. All complications occurred more frequently in patients with 2DE-detected vegetations. When eight patients with known or suspected right-sided endocarditis were excluded, the difference in complica-

Table I. Infective organism

Organism	No.
Streptococcus	16 (32%)
S. viridans	10
Enterococcal	5
Microaerophilic	1
Staphylococcus	25 (50%)
S. aureus	21
S. epidermidis	4
Other	7 (14%)
Pseudomonas	5
Hemophilus	1
E. coli	1
Negative	2 (4%)

Table II. Study population following echocardiography

	Vegetation (n = 21)	No vegetation (n = 29)
Sex distribution		
Male	13 (62%)	16 (55%)
Female	8 (38%)	13 (45%)
Age (yr) (range)	43 (19-83)	41 (21-83)
Predisposing factors		
Intravenous drug abuse	5 (24%)	14 (48%)
Rheumatic disease	1 (5%)	5 (17%)
Degenerative/congenital aortic valve	3 (14%)	2 (7%)
Mitral valve prolapse	4 (19%)	1 (3%)
Infective organism		
Streptococcus	10 (48%)	6 (21%)
Staphylococcus	8 (38%)	17 (59%)
Other	2 (10%)	5 (15%)

tion rates between patients with and without vegetations was even more apparent (Table IV). Of the five patients who died with evidence of vegetation, the cause of death was embolus in two, myocardial infarction in one, and multiple organ failure in two. One patient without a vegetation died and his death was related to multiple organ failure. In the 10 patients with vegetations and arterial emboli, the embolus was cerebral in seven and peripheral in three. In the four patients with embolic phenomena without vegetations, the embolus was cerebral in two and peripheral in two. In the five patients with serial 2DE studies, the mean vegetation size was 0.8 cm^2 (range 0.2 to 1.3 cm^2) prior to the embolus and 0.4 cm^2 (range 0 to 0.5 cm^2) following embolization. The vegetation disappeared completely in three of these five patients.

Valvular surgery was performed in nine patients with vegetations and six patients without vegetations. In the vegetation subgroup, the indication for surgery was congestive heart failure in seven and severe aortic regurgitation in two. In those without vegetation, the reason for surgery was congestive heart failure in four and severe aortic regurgitation in two. The relationship of the site of vegetation to complications is outlined in Table V. All five deaths occurred in patients with aortic vegetations. There were no complications in the three patients with tricuspid vegetations. The relationship between the size of the left-sided vegetation and complications is summarized in Table VI. Patients with vegetations greater than 1.0 cm^2 had a higher prevalence of death, congestive heart failure, and surgical intervention.

Table III. Complications

	Vegetation (n = 21)	No vegetation (n = 29)
Death	5 (24%)	2 (7%)
Congestive heart failure	8 (38%)	6 (21%)
Surgery	9 (43%)	5 (24%)
Embolus	10 (48%)	4 (14%)
Any complication	18 (86%)	18 (62%)

Table IV. Complications excluding known/suspected right-sided endocarditis (n = 8)

	Vegetation (n = 18)	No vegetation (n = 24)
Death	5 (28%)	1 (4%)
Congestive heart failure	8 (44%)	6 (25%)
Surgery	9 (50%)	6 (25%)
Embolus	10 (56%)	6 (25%)
Any complication	18 (100%)	16 (67%)

COMMENTS

Our data support the concept that echocardiographically detected vegetation identifies a subgroup of patients with infective endocarditis who are at high risk of life-threatening complications. Wann et al.[3] initially suggested that echocardiography could not only detect vegetations but could define a subgroup of patients with infective endocarditis who had a higher prevalence of complications. A number of subsequent studies have concurred with Wann's conclusions.[9-13] When our data are pooled with these other studies (Table VII), it is evident that patients with infective endocarditis and echo-detected vegetations are at least twice as likely to have a serious complication compared to those without vegetation. The variability of complication rates from study to

Table V. Relationship of site of vegetation to complications

	Aortic (n = 10)	*Mitral (n = 8)*	*Tricuspid (n = 3)*
Death	5 (50%)	0	0
Congestive heart failure	4 (40%)	4 (50%)	0
Surgery	6 (60%)	3 (38%)	0
Embolus	5 (50%)	5 (63%)	0

Table VI. Relationship between size of left-sided vegetation and complications

	Large (>1.0 cm²) (n = 11)	*Small (<1.0 cm²) (n = 7)*
Death	4 (36%)	1 (14%)
Congestive heart failure	7 (64%)	1 (14%)
Surgery	6 (55%)	3 (43%)
Embolus	6 (55%)	4 (57%)

Table VII. Echocardiographic reports on complications in infective endocarditis

Report	*Death (%)*	*CHF (%)*	*Embolus (%)*	*Surgery (%)*
Vegetation present				
Wann et al.,[3] 1976 (n = 22)	9	100	18	82
Davis et al.,[9] 1980 (n = 17)	35	47	82	100
Stewart et al.,[10] 1980* (n = 47)	11	30	30	25
Hickey et al.,[11] 1981 (n = 22)	36	81	50	64
Markiewicz et al.,[12] 1983 (n = 7)	86†	86	29	N/R
O'Brien and Geiser,[13] 1984* (n = 23)	22	83	37	65
Present study* (n = 21)	24	38	48	43
Total (n = 159)	23	66	42	63
Vegetation absent				
Wann et al.,[3] 1976 (n = 43)	0	28	0	0
Davis et al.,[9] 1980 (n = 13)	23	15	46	15
Stewart et al.,[10] 1980* (n = 40)	5	2	5	10
Hickey et al.,[11] 1981 (n = 14)	14	29	36	21
Markiewicz et al.,[12] 1983 (n = 18)	33†	28	17	N/R
O'Brien and Geiser[13], 1984* (n = 8)	25	50	0	25
Present study* (n = 29)	7	21	14	24
Total (n = 165)	12	25	17	16

CHF = congestive heart failure; N/R = not reported.
*2DE studies.
†Death and surgery combined; data not used in total calculation.

study is not unexpected, since patients with infective endocarditis represent a heterogeneous population in terms of age, underlying cardiac disease, and virulence of the infective organism. In addition, there continue to be institutional differences in the precise indication and timing of surgical intervention which further contribute to this variability. Nevertheless, our experience in combination with these other studies[3, 9-13] emphasizes the importance of echocardiography in identifying a potentially high-risk population which requires careful monitoring for early intervention.

Our study, as well of those of Stewart et al.[10] and O'Brien and Geiser,[11] primarily used 2DE techniques. Other studies which have examined the relationship of vegetations to complications[3, 9, 11, 12] used M-mode, or unidimensional, echocardiography. The development of 2DE techniques has allowed better characterization and localization of the vegetative lesions. Although some studies comparing M-mode and 2DE have reported a better sensitivity of 2DE vegetation detection,[8] other reports[5, 7] have found the two techniques to be equally sensitive and suggest that the primary advantage of 2DE is the ability to more comprehensively delineate the vegetation on both left-sided and right-sided valves. Our incidence of vegetations was generally lower than that reported in previous studies. This is most likely related to the strict 2DE criteria we used to define a vegetation which improved the specificity of the diagnosis. The finding of valve thickening unrelated to a vegetative process was not infrequent in our series, since most of our patients had some form of underlying valvular disease. Thus, to avoid a diagnosis of vegetative endocarditis in these patients, more rigorous criteria were employed. Although we could not exclude a diagnosis of vegetations in these patients with underlying valvular disease, our data suggest that specificity of diagnosis may be of equal or greater importance in prognostication than sensitivity.

Our data further suggest that vegetation size, which can be measured by 2DE, may be an additional risk factor for complications. In our study, patients with vegetations greater than 1 cm^2 had more frequent death, heart failure, and surgery than those with smaller vegetations. The risk of embolization, however, did not appear to be related to the size of the echo-detected vegetation. These results differ from the experience of Stewart et al.,[10] who found that vegetation size was not predictive of clinical outcome. This apparent discrepancy may be related to methodologic differences. Stewart et al.[10] used three vegetation size categories based on unidimensional measurements, whereas we used two categories based on two-dimensional measurements. In addition, they did not present their results to assess possible trends toward an increased complication rate.

In our study, the site of the vegetation had prognostic importance. All five deaths in patients with 2DE-detected vegetations occurred in patients with aortic vegetations. However, both the mitral and aortic sites predisposed patients to a high risk of complications. On the other hand, none of the three patients with tricuspid vegetation had a serious complication. This is in keeping with the more benign course of vegetative endocarditis in patients with intravenous drug abuse.[16]

Despite the ability of 2DE to identify high-risk subgroups, on the basis of our data, we cannot recommend surgical intervention solely on the basis of the visualization of a vegetative mass on 2DE. The decision to intervene surgically must continue to be based on the entire clinical picture with emphasis on hemodynamic instability. Clearly, however, patients with 2DE-detected vegetations require careful and intensive monitoring since they are at high risk of in-hospital complications.

SUMMARY

Although 2DE is considered the most sensitive method for detecting vegetations in infective endocarditis, the independent clinical significance of these vegetations continues to be debated. To further examine this, we identified 74 patients who were diagnosed as having infective endocarditis over a 54-month period. The 50 patients who underwent 2DE examination form the basis of this report. Definite vegetations were present in 21 (42%) patients and measured 1.2 ± 0.2 cm^2. The vegetation was localized to the aortic valve in 10 patients, the mitral valve in eight, and the tricuspid valve in three. A major complication, defined as death, new-onset congestive heart failure, major arterial embolus, or valve surgery occurred in 86% of the vegetative endocarditis patients compared to 62% of those without vegetations. Among those patients with vegetations, death occurred in 24%, heart failure in 38%, arterial embolus in 48%, and surgery in 43%. This compared to 7%, 21%, 21%, and 24%, respectively, in those patients without vegetations. These data support the concept that 2DE detection of a vegetation defines a high-risk subgroup of patients with infective endocarditis in whom careful monitoring and aggressive management are warranted.

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REFERENCES

1. Osler W. Gulstonian lectures on malignant endocarditis. Lancet 1885;1:459.
2. Dillon JC, Feigenbaum H, Konecke LL, Davis RH, Chang S. Echocardiographic manifestations of valvular vegetations. AM HEART J 1973;86:698.
3. Wann LS, Dillon JC, Weyman AE, Feigenbaum H. Echocardiography in bacterial endocarditis. N Engl J Med 1976;295:135.
4. Roy P, Tajik A, Guilianl ER, Schattenberg TT, Gau GT, Frye RL. Spectrum of echocardiographic findings in bacterial endocarditis. Circulation 1976;53:474.
5. Mintz GS, Kotler MN, Segal BL, Parry WR. Comparison of two dimension and M mode echocardiography in the evaluation of patients with infective endocarditis. Am J Cardiol 1979;43:738.
6. Gilbert BW, Haney RS, Crawford F, et al. Two-dimensional echocardiographic assessment of vegetative endocarditis. Circulation 1977;55:346.
7. Wann LS, Hallam CC, Dillon JC, Weyman AE, Feigenbaum H. Comparison of M-mode and cross-sectional echocardiography in infective endocarditis. Circulation 1979;60:728.
8. Martin RP, Meltzer RS, Chia BL, Edward BS, Rakowski H, Popp RL. Clinical utility of two dimensional echocardiography in infective endocarditis. Am J Cardiol 1980;46:379.
9. Davis RS, Strom JA, Frishman W, et al. The demonstration of vegetations by echocardiography in bacterial endocarditis. Am J Med 1980;69:57.
10. Stewart JA, Silimperl D, Harris P, Wise NK, Fraker TD Jr, Kisslo JA. Echocardiographic documentation of vegetative lesions in infective endocarditis: Clinical implications. Circulation 1980;61:374.
11. Hickey AJ, Wolfers J, Wilcken DEL. Reliability and clinical relevance of detection of vegetations by echocardiography in bacterial endocarditis. Br Heart J 1981;46:624.
12. Markiewicz W, Moscowitz M, Edonte Y, Finklestein R, Rax R. Prognostic implication of detecting vegetations by M-mode echocardiography. Cardiology 1983;70:194.
13. O'Brien JT, Geiser EA. Infective endocarditis and echocardiography. AM HEART J 1984;108:386.
14. Clemens JD, Horwitz RI, Jaffe CC, Feinstein AR, Stanton BF. A controlled evaluation of the risk of bacterial endocarditis in persons with mitral valve prolapse. N Engl J Med 1982;307:776.
15. The American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. Circulation 1980;62:212.
16. Panidis IP, Kotler MN, Mintz GS, Segal BL, Ross JJ. Right heart endocarditis: Clinical and echocardiographic features. AM HEART J 1984;107:759.