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CLINICAL STUDIES

Diagnostic Value of Transesophageal Compared With Transthoracic Echocardiography in Infective Endocarditis

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To compare the diagnostic value of transesophageal and transthoracic echocardiography in infective endocarditis, paired transesophageal and transthoracic echocardiograms were obtained prospectively for 66 episodes of suspected endocarditis in 62 patients. Echocardiographic results were compared with the presence or absence of endocarditis determined by pathologic or nonechocardiographic data from the subsequent clinical course. All echocardiograms were interpreted by an observer told only that the studies were from patients in whom the diagnosis of endocarditis was suspected.

The diagnosis of endocarditis was eventually made in 16 of the 66 episodes of suspected endocarditis (14 by pathologic and 2 by clinical criteria). In 7 of 16 transthoracic and 15 of 16 transesophageal echocardiograms, endocarditis was diagnosed at a probability level of "almost certain," giving a sensitivity of 44% and 94%, respectively ($p < 0.01$). For the remaining episodes, 49 of 50 transthoracic and all transesophageal studies yielded normal results, giving a specificity of 98% and 100%, respectively.

This study suggests that transesophageal echocardiography is highly sensitive and specific for the diagnosis of infective endocarditis and significantly more sensitive than transthoracic echocardiography. Although echocardiography cannot rule out endocarditis, the high diagnostic sensitivity of transesophageal echocardiography results in a low probability of the disease when the study yields negative results in a patient with an intermediate likelihood of the disease.

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Transthoracic echocardiography is useful in patients with infective endocarditis to detect vegetations and assess the extent and hemodynamic sequelae of valvular damage. However, low diagnostic sensitivity has limited the value of echocardiography in patients in whom endocarditis is suspected but not certain (1–3). Suboptimal patient imaging and limited instrument resolution are major obstacles to the application of transthoracic echocardiography for this purpose. In contrast, transesophageal echocardiography yields consistently high quality images of the mitral, aortic and tricuspid valves and may be superior to transthoracic echocardiography in the diagnosis of intracardiac masses such as vegetations from infective endocarditis (4–8).

To estimate the diagnostic value of transesophageal versus transthoracic Doppler color flow echocardiography in patients with suspected infective endocarditis, we compared echocardiographic results with the final diagnosis from pathologic findings or nonechocardiographic data from the patient's clinical course. Because the echocardiographic diagnosis of endocarditis may be influenced by prior clinical information, the echocardiograms were read at another institution by an experienced interpreter told only that the patients were suspected of having endocarditis.

Possible false positive findings are of concern with the introduction of an improved method of diagnostic imaging such as transesophageal echocardiography. To determine the ability of the method of echocardiographic interpretation used in this study to differentiate normal variant findings from valvular abnormalities, 16 healthy volunteers were also studied by transthoracic and transesophageal echocardiography.

Methods

Study patients. From January 1988 to October 1989, all patients referred to the Albuquerque Veterans Affairs Medical Center Echocardiography Laboratory were screened and 62 consecutive patients meeting specific criteria for the suspicion of endocarditis were entered into this study. These criteria were a documented orally measured body temperature of ≥100°F and one or more of the following: a murmur, a valve prosthesis, a history of recent intravenous drug abuse or known infection by an organism frequently associated with infective endocarditis. Patients meeting these criteria underwent paired transthoracic and transesophageal Doppler color flow echocardiographic studies, usually on the same day, according to the guidelines of the institutional

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Table 1. Clinical Characteristics of 62 Study Patients

Mean age (yr)	53
Men (no.)	54
Fever (%)	100
Murmur (%)	98
Left ventricular outflow (%)	54
Regurgitation (%)	44
Prosthesis (%)	18
IV drug abuse (%)	23
Positive blood cultures (%)	60
Mean illness duration before TEE (days)	42

IV = intravenous; TEE = transesophageal echocardiography.

Table 2. Findings in 16 Patients With Endocarditis

Diagnostic criteria	
Surgical/autopsy confirmation	14
New murmur and positive blood cultures	2
Valves involved	
Aortic only	5
Mitral only	7
Prosthesis	3
Aortic and tricuspid	1
Organism*	
Staphylococcus aureus	6
Streptococcus viridans	3
Enterococcus, Hemophilus parainfluenzae, Lactobacillus, Streptococcus equinus, Pneumococcus, group B Streptococcus	1 each

*One patient with a negative culture had surgical confirmation.

Human Research Committee. All patients gave informed consent for the transesophageal study. The patients were followed up for a minimum of 8 weeks after the echocardiographic studies, with the exception of three patients lost to follow-up at 8 to 14 days. Thirteen patients with endocarditis underwent surgery and one patient died. Eight patients underwent early operation (2 to 20 days after study) and five responded initially to medical therapy but required operation after 3 to 15 months.

Presence or absence of endocarditis. The diagnosis of endocarditis was based on a previously published criterion (9–11) that is independent of the results of echocardiography. This criterion was the presence of either 1) surgical or autopsy confirmation, or 2) a new or changing murmur with either a) positive blood cultures, b) peripheral stigmata of endocarditis (for example, embolic phenomena), or c) supportive laboratory evidence (for example, positive rheumatoid factor). At the end of the study, all patients with endocarditis met either condition 1 or condition 2a. No patient had positive blood cultures or peripheral stigmata or laboratory data suggesting endocarditis in the absence of a new or changed murmur. Patients were classified as not having endocarditis if the criterion was not met during the follow-up period. Table 1 shows the clinical characteristics of the 62 study patients. Tables 2 and 3 summarize data for patients with and without endocarditis.

Echocardiography. Because 4 patients were referred twice during the study period for the suspicion of endocarditis, 66 pairs of echocardiograms were performed in 62 patients. The mean interval between studies was 1.2 days (range 0 to 7). Eighty-four percent of paired studies were performed within 24 h of each other; 15 of the 16 paired studies in patients eventually found to have endocarditis were done within 24 h.

Transesophageal examinations were performed using a 5-MHz gastroscope-mounted transducer interfaced with the 77020A system (Hewlett-Packard). Before transesophageal study, all patients fasted for ≥4 h and received lidocaine throat spray and intravenous diazepam (2.5 to 10 mg) and meperidine (25 to 75 mg). No complications were encountered in examinations ranging from 15 to 45 min in duration.

Examination of the cardiac valves was performed at minimal possible depth settings (6 to 12 cm) over multiple scan planes obtained by alternately withdrawing and advancing the transesophageal probe. With the exception of the pulmonary valve, each valve was examined by M-mode echocardiography at 100 cm/s sweep speed and Doppler color flow mapping. Transesophageal echocardiography in healthy volunteers was performed with use of the same protocol used for patients with suspected endocarditis.

Transthoracic examinations were performed as appropriate for patients with possible endocarditis and included the detailed examination of each cardiac valve by M-mode, two-dimensional and Doppler color flow mapping at minimal depth settings. Both 2.5- and 5-MHz transducers were used in most studies.

Analysis of echocardiograms. Echocardiograms from patients and healthy volunteers were randomized, copied in their entirety on separate sets of transthoracic and trans-

Table 3. Findings in 46 Patients Without Endocarditis (50 febrile episodes)

	No.
Positive blood culture	22 (44%)
Staphylococcus aureus	6
Staphylococcus epidermidis	4
Enterococcus	2
Polymicrobial	2
Alpha-hemolytic *Streptococcus*	2
Pseudomonas	1
Streptococcus constellatus	1
Peptostreptococcus	1
Streptococcus anginosus	1
Clostridium perfringens	1
Diphtheroids	1
Noncardiac source of fever	42 (84%)
Antibiotic therapy ≥10 days*	7 (14%)
Staphylococcus aureus	4
Polymicrobial	2
Streptococcus anginosus	1

*This therapy may be considered effective against endocarditis. Treatment decisions were at the primary physician's discretion.

Table 4. Valve Leaflet Visualization in 66 Echocardiographic Studies

	Echocardiograms With "Average" or "Better Than Average" Image	
	Transesophageal (%)	Transthoracic (%)
Tricuspid valve	83	82
Mitral valve	100*	89
Aortic valve	96†	68

*$p < 0.06$, †$p < 0.01$ compared with transthoracic echocardiography.

esophageal tapes and sent to an experienced echocardiographer at an institution in another city. The interpreter was told only that all subjects met the inclusion criteria for suspected infective endocarditis. The interpreter did not know which transthoracic and transesophageal studies were paired.

Interpretation followed a format for the scoring of relevant cardiac structures in several categories. The adequacy of valve visualization was scored on a scale from 1 to 3 (1 = well seen (average or better), 2 = seen less well than average and 3 = not imaged). Cardiac structures were classified as normal or abnormal, with the abnormality specified, and each study was assigned an overall rating of the probability of endocarditis. The rating categories for probability of endocarditis were 1 = very low, 2 = possible, 3 = probable and 4 = almost certain. A rating of very low probability of endocarditis was assigned to normal studies. A rating of possible endocarditis was assigned to studies showing abnormalities representing a possible site of infection, such as degenerative changes, mitral valve prolapse or a valve prosthesis. A probable rating was assigned to studies with strongly suggestive findings, such as a flail leaflet or nonspecific localized leaflet or chordal thickening suggesting vegetation. A rating of almost certain endocarditis was given in the presence of a mass typical for a vegetation or evidence of leaflet perforation or annular abscess. Characteristics of a vegetation are soft tissue reflectance, irregular geometry, free mobility and attachment to leaflets, chordae or chamber walls.

Statistics. The statistical significance of differences in sensitivity, specificity, predictive value and the frequencies of findings by the two echocardiographic methods were tested for significance with use of a two-tailed Fisher's exact test.

Results

Leaflet visualization. To compare valve imaging by the two echocardiographic methods, the frequencies of valves scored as imaged with average or better quality are shown in Table 4. The data suggest that the transesophageal method provides imaging of both mitral and aortic leaflets superior to that of transthoracic echocardiography. Conversely, no difference was shown for tricuspid valve imaging by the two methods.

Valvular abnormalities. Table 5 shows the high frequency of morphologic valve abnormalities demonstrated by transesophageal and transthoracic echocardiography in patients with suspected endocarditis. In two patients, aortic valve imaging by transthoracic echocardiography did not permit discrimination of a bioprosthesis from severe aortic valve sclerosis by an independent interpreter (all prostheses were correctly identified by transesophageal echocardiography). In patients without endocarditis, the interpreter noted thickening of the anterior mitral valve leaflet (believed to be abnormal) significantly more often by transthoracic than by transesophageal echocardiography.

Valve regurgitation. Table 6 shows the frequency and degree of valve regurgitation detected by the two echocardiographic methods. Although transesophageal echocardiography demonstrated valve regurgitation more often, this difference was limited to lesions of trivial or mild severity.

Diagnosis of infective endocarditis. The sensitivity and specificity of transesophageal and transthoracic echocardiography for the diagnosis of infective endocarditis are shown in Table 7 for two different definitions of a positive echocardiogram. When an almost certain probability of endocarditis is considered positive (upper panel), only 7 (44%) of 16 transthoracic studies were positive compared with 15 (94%) of 16 transesophageal studies ($p < 0.01$). When a lesser degree of certainty is used to define a positive echocardiogram (lower panel of Table 7), transesophageal echocardiography still shows a higher sensitivity than the transthoracic study. Specificity was high and very similar for the two methods.

Table 5. Echocardiographic Valve Morphology in 66 Echocardiographic Studies

	Thickening		Prolapse		Prosthesis		Mass	
	TEE	TTE	TEE	TTE	TEE	TTE	TEE	TTE
Tricuspid valve	2	3	4	0	—	—	1	1
Mitral valve	7*	17	11	8	5	5	8	6
Aortic valve	21	22	0	2	9†	7	7	2

*$p < 0.05$ compared with transthoracic echocardiography. †Two aortic bioprostheses were not distinguished from sclerosis by transthoracic echocardiography. TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

Table 6. Valve Regurgitation in 66 Echocardiographic Studies

	Trivial		Mild		More Than Mild		Total		% Total	
	TEE	TTE	TEE	TTE	TEE	TTE	TEE	TTE	TEE	TTE
Tricuspid valve	6	5	8	13	8	11	22	29	33	44
Mitral valve	16*	2	9	11	17	14	42†	27	64	41
Aortic valve	7	2	6	4	9	11	22	17	33	26

*$p < 0.001$, †$p < 0.05$ compared with transthoracic echocardiography. Abbreviations as in Table 5.

Causes of false positive and false negative echocardiograms. Table 8 lists the probable causes of misdiagnosis for the one false positive and nine false negative transthoracic echocardiograms and one false negative transesophageal echocardiogram; five of the false negative transthoracic studies occurred in the setting of accompanying valvular disease (Fig. 1 and 2) and four with an apparently normal valve (Fig. 3). Of 13 episodes of suspected endocarditis in patients with a prosthesis, all 3 episodes diagnosed as endocarditis were falsely negative by transthoracic echocardiography, but were positive by transesophageal study.

Echocardiography in healthy volunteers. The transthoracic echocardiograms of 14 of the 16 healthy volunteers (26 to 41 years of age) were classified as normal. Two were interpreted as showing possible endocarditis on the basis of redundant, hypermobile mitral chordae tendineae in one and a thickened aortic valve in the other. The transesophageal echocardiograms were also interpreted as normal except in two other subjects. These two studies were interpreted as showing possible endocarditis, one because of redundant mitral chordae and the other because of a thin, "hair-like" structure prolapsing below the aortic valve accompanied by slight aortic regurgitation. Similar and thin 2- to 4-mm strands were noted in two (20%) of other healthy volunteers and in six patients (10%) with suspected endocarditis.

Discussion

Major findings. There are two major findings in this study: Transesophageal echocardiography 1) shows a high sensitivity for the diagnosis of endocarditis in patients suspected of having the disease, and 2) offers a significant improvement in sensitivity over transthoracic echocardiography for this diagnosis. For a diagnostic test in patients with suspected endocarditis, sensitivity is an important test characteristic because of the serious consequences of missing the disease and delaying therapy. In this study (with a 24% prevalence of endocarditis), the high sensitivity of transesophageal echocardiography results in a 98% negative predictive value (the probability of no endocarditis if the patient has a negative test) compared with an 84% value for transthoracic echocardiography ($p < 0.05$). In addition, with the method of echocardiographic interpretation used in this study, false positive findings are unusual by either method.

Bias in previous studies. Estimates of sensitivity range from 18% to 90% in prior studies (1–3, 12–21) of echocardiography in the diagnosis of endocarditis, reflecting the importance of factors affecting the diagnostic performance of echocardiography in patients with the disease. Variable clinical information available at the time of echocardiographic interpretation and variation in the type of disease in the study group (spectrum bias) probably account for this wide range (12). In most series (5,15–19), the question of interpreter bias is dealt with ambiguously or not at all. By not using specific inclusion criteria or by using retrospective data, most studies (16–22) of echocardiography in endocarditis have been subject to spectrum bias. In general, prospective studies (1,2) have given estimates of the sensitivity for transthoracic echocardiography similar to that of the present study if a rating of almost certain is considered positive for endocarditis (44%). Sensitivity in the present study is higher (67%) and more in line with other recent data

Table 7. Comparison of Transesophageal and Transthoracic Echocardiography: Sensitivity and Specificity

	Sensitivity	Specificity
If Rating 4 (almost certain) is considered diagnostic		
Transesophageal	94%* (15/16)	100% (50/50)
Transthoracic	44% (7/16)	98% (49/50)
If Rating 3 or 4 (probable or almost certain) is considered diagnostic		
Transesophageal	94% (15/16)	98% (49/50)
Transthoracic	69% (11/16)	92% (46/50)

*$p < 0.01$ compared with transthoracic echocardiography.

Table 8. Causes of False Positive and False Negative Echocardiograms

	No. of Pts	Apparent Cause
False negative		
TTE	2	Myxomatous disease
	3	Valve prosthesis
	4	Vegetation small, valve otherwise normal
TEE	1	Ruptured chord (no vegetation seen)
False positive		
TTE	1	Sclerosis limited to leaflet tips (rheumatic)

A rating of almost certain was required for the echocardiogram to be considered positive. Pts = patients; other abbreviations as in Table 5

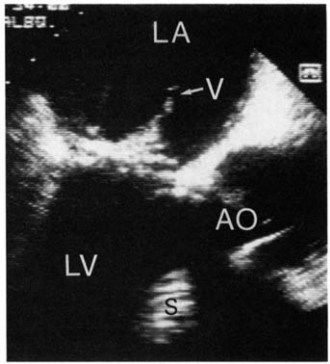


Figure 1. Infected mitral bioprosthesis. This systolic transesophageal view shows a mass (V) attached to the bioprosthetic sewing ring and prolapsing into the left atrium (LA). The image plane is positioned between the bioprosthetic struts, which are not shown. The distance between diagonal dots along the side of the left atrium is 1 cm. Transthoracic examination of the prosthesis failed to demonstrate this mass, primarily because of acoustic shadowing from the struts and sewing ring. AO = aortic valve; LV = left ventricle; S = interventricular septum.

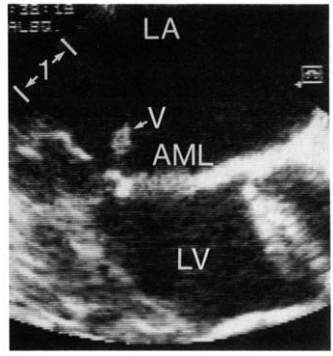


Figure 2. Small mitral vegetation. The transesophageal image plane is tangential to the mitral anulus, showing a truncated view of the left ventricle (LV). A small mass (V) is tethered from the tip of the anterior mitral leaflet (AML) and prolapses into the left atrium (LA). In real time, this mass showed rotatory motion independent of the leaflet. A 1-cm distance is indicated diagonally to the left.

(16–19,22) if studies classified as indicating probable endocarditis are included as positive for endocarditis.

An early series by Erbel et al. (5) included direct comparison of transesophageal and transthoracic imaging. Their results were generally similar to those of the present study, but the clinical applicability of their data is uncertain because of ambiguity regarding how endocarditis was diagnosed, the selected group of patients with the disease and the calculation of sensitivity and specificity from two different patient groups.

Bias in the present study. In the present study, many sources of bias were eliminated or controlled. Interpreter bias was controlled by establishing a uniform bias regarding the probability of endocarditis for the echocardiograms. The interpreter's expectations approximated those that apply when echocardiograms are done in clinical practice as an independent test for endocarditis. The interpreter did not have access to other clinical information about the patients.

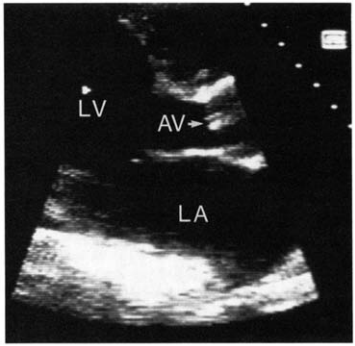
The effects of spectrum bias in the present study were partially controlled by the prospective inclusion of consecutive patients meeting specific criteria for the suspicion of infective endocarditis. It seems prudent to limit transesophageal echocardiography to patients with a significant clinical suspicion of endocarditis. Because similar constraints on the use of this procedure should hold true in clinical practice, our results should be broadly relevant.

Nevertheless, patients were entered into the present study only after referral (not usually from the emergency room) and 40% were patients from other hospitals. The clinical spectrum of disease is thus likely to be representative of a referral hospital. Our study group may be weighted in favor of patients with more advanced disease because 14 of 16 patients eventually underwent surgery. However, surgery was performed late only after initial success of medical therapy in five patients. In addition, the diagnosis of endocarditis was not established before echocardiography in 9 of the 16 patients.

This study may have been biased by the inclusion of seven patients classified as not having endocarditis who received treatment usually effective for the disease, possibly preventing the development of evidence of endocarditis (Table 3). However, if these patients are excluded from analysis, the results of this study, including the significance levels for differences between transesophageal and transthoracic echocardiography, are essentially unchanged.

Strict criteria were used in this study for the diagnosis of endocarditis. It is possible that some patients were misclassified as not having the disease. If so, the results of this study would still strongly support the diagnostic superiority of transesophageal echocardiography, but its sensitivity would be lower. It seems appropriate to caution against efforts to completely exclude endocarditis by this means. This point is reinforced by our finding of one false negative transesophageal echocardiogram in this study.

Finally, the excellent diagnostic performance of trans-



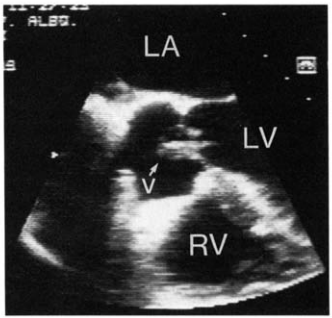


Figure 3. Infected aortic valve. **Top panel.** Transthoracic parasternal long-axis view in a patient with suspected infective endocarditis shows only nodular thickening of the aortic leaflet tip (AV). No mass distinct from the valve itself was seen. This echocardiographic study was rated as showing possible endocarditis. **Bottom panel.** Transesophageal image in the same patient. The valve demonstrates key features not evident on transthoracic study. 1) The leaflets appear normal near the anulus (making degenerative change unlikely); 2) the leaflet thickening (V) has soft tissue reflectance; and 3) a small portion of the mass prolapses into the left ventricular (LV) outflow tract. Diastolic fluttering of this thin extension of the mass was readily demonstrated. The distance between diagonal dots at the upper right of the image is 1 cm. This study was rated as showing almost certain endocarditis. RV = right ventricle; other abbreviations as in Figure 1.

esophageal echocardiography in the present study may reflect in part the expertise of the experienced operators and interpreter. Replication of these results may require the accumulation of experience in this method of echocardiography.

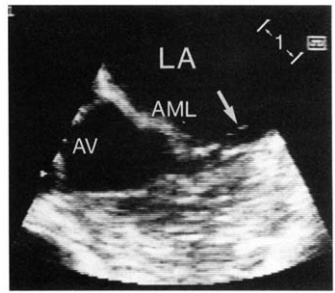


Figure 4. Mitral valve in a normal volunteer. The transesophageal image plane is tangential to the mitral anulus, so that the posterior leaflet appears very short. A thin strand (arrow) prolapses into the left atrium (LA) from the tip of the anterior mitral leaflet (AML). A 1-cm distance is indicated diagonally to the right of the left atrium. AV = aortic valve.

Potential false positive findings. Our experience with this technique suggests that false positive findings could occur, even though the expert interpreter in this study did not diagnose any transesophageal echocardiograms as falsely positive. The tiny mobile strands below the aortic valve might be mistaken for small vegetations, but probably represent prominent Lambl's excrescences.

Other potential false positive findings we observed include strands extending from prosthetic sewing rings, hypermobile and redundant mitral chordae tendineae, localized chordal thickening and false chordae in the left ventricular outflow tract. We also observed brightly reflectant, transient echoes on the left atrial side of the mitral valve during early systole in 3 (5%) of the 62 patients with suspected endocarditis and 3 (17%) of the 16 healthy volunteers (Fig. 4).

Clinical implications. In this prospective study, transesophageal echocardiography showed high sensitivity for the diagnosis of endocarditis and appeared to represent a significant advance over transthoracic echocardiography. This superior diagnostic sensitivity applied to patients with minimal underlying valve disease as well as to patients with preexisting abnormalities such as a prosthesis. A high level of diagnostic specificity can be achieved by both echocardiographic methods.

To decide whether transesophageal echocardiography will be useful to rule out endocarditis, the clinician should consider the degree of suspicion of the disease. If suspicion is high, a negative transesophageal echocardiogram will not obviate the need for therapy. Conversely, if suspicion is intermediate or low, a negative study may allow time for obtaining additional blood cultures and other clinical data.

The management of many patients in our study was affected by transesophageal echocardiographic findings clas-

sified as positive for endocarditis when transthoracic study was inconclusive. Of the nine patients with endocarditis classified as having almost certain endocarditis by transesophageal echocardiography, five were classified only as having possible endocarditis by transthoracic study (with the other four classified as having probable endocarditis). Furthermore, in four of these five with a rating of possible disease, transesophageal findings led to early operation in two patients. Transesophageal echocardiography thus also appears to be useful when the clinical suspicion of endocarditis is intermediate or high but results of a transthoracic study are uncertain.

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