An Approach to Improve the Negative Predictive Value and Clinical Utility of Transthoracic Echocardiography in Suspected Native Valve Infective Endocarditis

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Background: In patients with suspected native valve infective endocarditis, current guidelines recommend initial transthoracic echocardiography (TTE) followed by transesophageal echocardiography (TEE) if clinical suspicion remains. The guidelines do not account for the quality of initial TTE or other findings that may alter the study's diagnostic characteristics. This may lead to unnecessary TEE when initial TTE was sufficient to rule out vegetation.

Methods: The objective of this study was to determine if the use of a strict definition of negative results on TTE would improve the performance characteristics of TTE sufficiently to exclude vegetation. A retrospective analysis of patients at a single institution with suspected native valve endocarditis who underwent TTE followed by TEE within 7 days between January 1, 2007, and February 28, 2014, was performed. Negative results on TTE for vegetation were defined by either the standard approach (no evidence of vegetation seen on TTE) or by applying a set of strict negative criteria incorporating other findings on TTE. Using TEE as the gold standard for the presence of vegetation, the diagnostic performance of the two transthoracic approaches was compared.

Results: In total, 790 pairs of TTE and TEE were identified. With the standard approach, 661 of the transthoracic studies had negative findings (no vegetation seen), compared with 104 studies with negative findings using the strict negative approach (meeting all strict negative criteria). The sensitivity and negative predictive value of TTE for detecting vegetation were substantially improved using the strict negative approach (sensitivity, 98% [95% CI, 95%–99%] vs 43% [95% CI, 36%–51%]; negative predictive value, 97% [95% CI, 92%–99%] vs 87% [95% CI, 84%–89%]).

Conclusions: The ability of TTE to exclude vegetation in patients is excellent when strict criteria for negative results are applied. In patients at low to intermediate risk with strict negative results on TTE, follow-up TEE may be unnecessary. (J Am Soc Echocardiogr 2016;29:315-22.)

Keywords: Infective endocarditis, Echocardiography, Transesophageal echocardiography, Screening

The diagnosis of infective endocarditis (IE) is based on the modified Duke criteria, among which the presence of endocardial vegetation on echocardiography is a major criterion.[1] Guidelines from multiple clinical societies, including the American College of Cardiology, the American Heart Association, and the Infectious Diseases Society of America, recommend transthoracic echocardiography (TTE) as the initial test when evaluating for vegetations in patients with a low or intermediate pretest probability of IE. Transesophageal echocardiography (TEE) is recommended to confirm absence of vegetations in patients with negative results on TTE if clinical suspicion of IE remains at least intermediate.[2,3]

These recommendations are based on work from the late 1980's and the 1990's showing that the sensitivity of TTE for detecting valvular vegetations (44%–75%) is markedly lower than what has been reported for TEE (>95%).[4-7] Most of the prior work reporting the diagnostic characteristics of TTE was performed with older generation echocardiographic technology. Furthermore, these recommendations are based strictly on the presence or absence of vegetation on TTE and do not account for image quality or other echocardiographic findings that may alter the study's diagnostic performance characteristics.

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Abbreviations

DELD = Duke Echocardiography Lab Database

IE = Infective endocarditis

NPV = Negative predictive value

TEE = Transesophageal echocardiography

TTE = Transthoracic echocardiography

The clinical utility of TTE would be markedly improved by increases in sensitivity and negative predictive value (NPV), which may allow negative results on TTE to exclude intracardiac vegetations. We hypothesized that using a set of strict criteria to identify studies with clearly normal results with adequate image quality would generate a subset of patients in whom negative results on TTE might obviate the need for follow-up TEE.

METHODS

Study Objective

The objective of this study was to determine whether implementing a strict definition of negative findings on TTE would improve the performance characteristics of TTE sufficiently to exclude vegetation.

Patient Population Derivation

The patient population was derived through a retrospective analysis of the Duke Echocardiography Lab Database (DELD). The setup of the DELD has been previously described.[8] Briefly, the DELD is a prospectively maintained digital archive of all echocardiograms obtained at Duke University Hospital and satellite clinics since 1995. This is linked to a corresponding searchable reporting database with clinical information derived from the electronic health record.

Patient Population

The DELD was searched for adult patients who underwent TTE followed by TEE within 7 days between January 1, 2007, and February 28, 2014. Patients who underwent the studies for any of the following indications were included: history of fever, bacteremia, and IE evaluation. The majority of transthoracic studies (>90%) were performed using the Philips iE33 platform (Philips Medical Systems, Andover, MA), which was fully integrated at our institution by January 1, 2007. The remaining studies were performed using the GE Vivid 7 or E9 platform (GE Healthcare, Little Chalfont, UK). Studies were performed using a 2.5-MHz phased-array probe.

The transthoracic echocardiographic imaging protocol for IE includes multiple zoomed-in views of each valve, two-dimensional sweeps of valves, the use of nontraditional windows to probe abnormal findings, and the use of fundamental frequencies to enhance spatial resolution beyond that of harmonic imaging alone. Patients with prior valve repair or replacement, complex congenital heart disease, prior heart transplantation, or left ventricular assist devices were excluded because of the higher incidence of IE and increased difficulty of imaging in these groups using TTE alone.[9-12] TEE was performed using the Philips iE33 machine and an omniplane 3.5-MHz phased-array probe using fundamental frequencies.

Definition of Vegetation

A vegetation was defined as an independently mobile or oscillating echogenic target or mass in a heart chamber or valve on an echocardiographic study done for one of the indications listed under "Patient Population." To identify studies showing vegetations, a string search was performed in the DELD on the "final interpretation" free-text field and valve comments fields for "vegetation," "target," "structure," "material," "strand," "density," and "mass." Misspellings were accounted for by using only the first few letters of each word to search, followed by a manual review of the results. Studies with mobile targets seen on a valve, without more likely alternative etiologies (e.g., senile degeneration, benign neoplasm, annular calcification), were considered suggestive of vegetation.[3] The results of follow-up TEE were considered the gold standard for presence of vegetation.

Strict Criteria for Negative Results on TTE

Two separate analyses were performed to evaluate the diagnostic characteristics of TTE in the evaluation of IE. In the first analysis, the standard definition of positive or negative results on TTE was used, based solely on the presence or absence of vegetation. For the second analysis, a strict definition of negative findings on TTE was developed, and studies not meeting these criteria were considered to have positive or indeterminate findings. The criteria for strict negative results on TTE are shown in Figure 1.

The strict negative criteria were designed to identify transthoracic echocardiograms that provide strong evidence against vegetation. Valvular regurgitation is characteristic of IE and has been associated with increased morbidity and mortality in patients diagnosed with IE.[1,13,14] Thus, studies with mild or greater regurgitation of any valve were labeled indeterminate. Because serial echocardiographic data may not be available for all patients presenting with suspected IE, the stability of regurgitant lesions was not included in the criteria.

Findings that suggest increased risk for IE were also exclusions in the strict negative criteria. These include valvular stenosis or sclerosis, intracardiac foreign bodies, and anatomic abnormalities such as ventricular septal defects and structural valvular disease, which have all been shown to increase the risk for IE.[10,15-22] Large or complex pericardial effusions were also excluded, because these have been associated with both increased rates of IE and worse outcomes when IE is present.[23,24]

Finally, all studies were required to have adequate technical quality to detect all components of the strict negative criteria, with moderate or better ultrasound quality defined as adequate visualization of anatomic structures, chamber morphology, endocardial borders, and cardiac function from the standard acoustic windows without the need for contrast.[25] Thus, studies without adequate image quality to detect the presence of valvular regurgitation, valvular sclerosis, or the presence of intracardiac hardware would be considered "poor" and not meeting the strict negative criteria. Ultrasound quality is graded at the time of clinical read for all echocardiographic studies performed in our laboratory. This grading, along with a search of all comments in the clinical report for "poor," "limited," or "inadequate" visualization of cardiac structures, was used to determine ultrasound quality for each echocardiogram.

Baseline Characteristics and Outcomes Data

Duke Enterprise Data Unified Content Explorer is a Web-based query tool used to extract data generated as a by-product of the care of patients in the Duke University Health System.[26] The cohort of patients generated from the initial query of the DELD was uploaded to Duke Enterprise Data Unified Content Explorer, and clinical data, including prior diagnoses, blood culture results, and outcomes data, were extracted. The available outcomes data applicable to this study were mortality and surgical intervention.

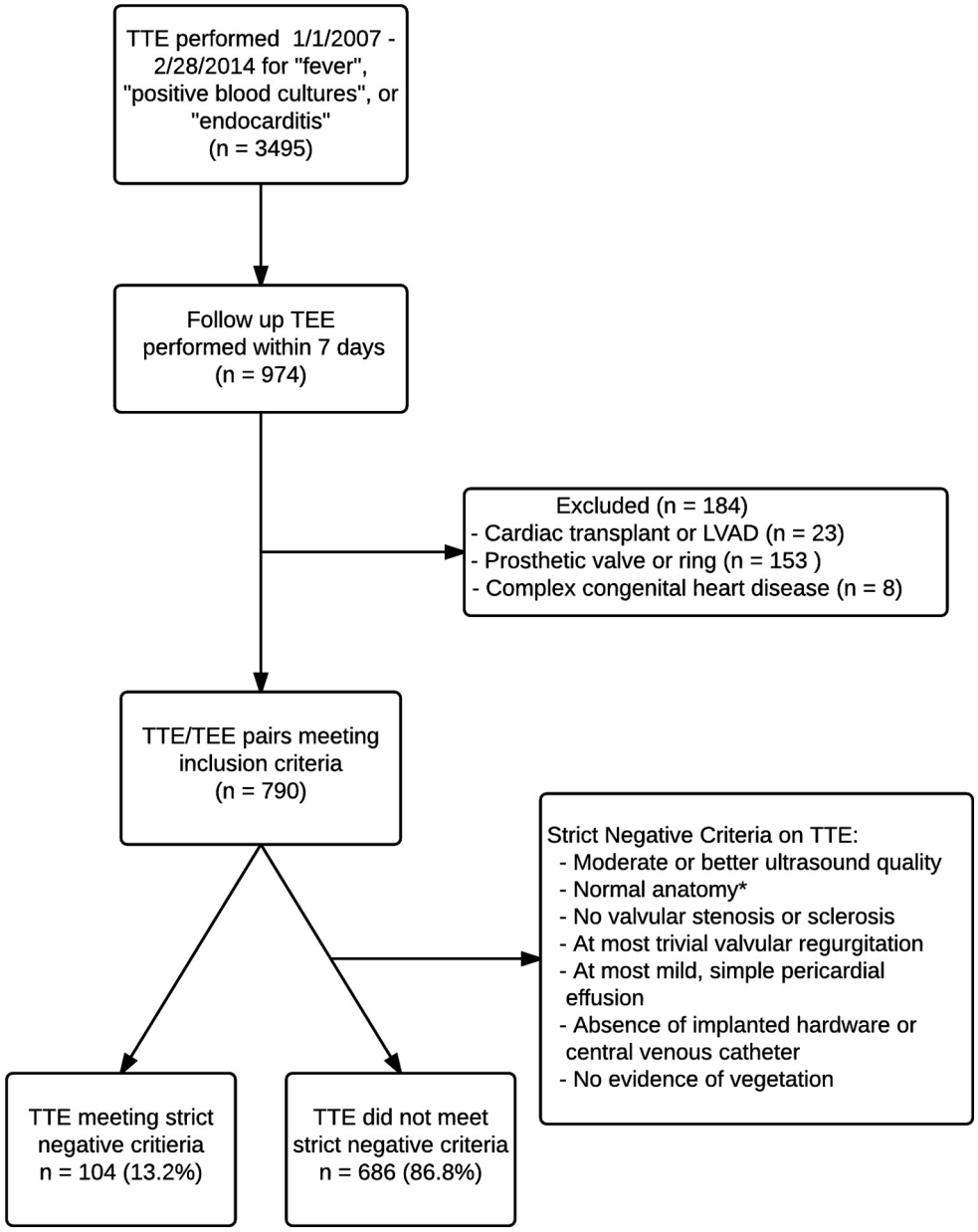

Figure 1 Study cohort derivation and strict negative criteria. This figure outlines the derivation of the study cohort and shows the list of strict negative criteria. LVAD, Left ventricular assist device. *Normal anatomy defined as tricuspid aortic, pulmonic, and tricuspid valves, mitral valve without mitral annular calcification, no mitral valve prolapse, no atrial septal defect or ventricular septal defect, repaired or unrepaired.

Statistical Analysis

The sensitivity (true positive/condition positive), specificity (true negative/condition negative), NPV (true negative/test outcome negative), and positive predictive value (true positive/test outcome positive) were determined for both the standard and strict negative approaches using the standard 2×2 table approach. Condition positive for both approaches was defined by the presence of vegetation on TEE. In the standard approach, test positive was defined by presence of vegetation on TTE, whereas in the strict negative approach, test positive was defined by TTE failing to meet all of the strict negative criteria (positive or indeterminate). Therefore, in the strict negative criteria approach, true positives were transthoracic studies with positive or indeterminate results that subsequently had positive findings on TEE, whereas true negatives were transthoracic studies that met the strict negative criteria and subsequently had negative findings on TEE (Figure 2B). Next, negative and positive likelihood ratios (false-negative rate/true-negative rate and true-positive rate/false-positive rate, respectively) and the resulting relationships for each approach between pretest and posttest odds using the Bayes theorem were determined. A test indication curve was then generated to compare the effect of the negative likelihood ratio on posttest probability using the two transthoracic echocardiographic interpretation approaches.[27] Differences in baseline characteristics between the strict negative subgroup and the positive or indeterminate subgroup were determined by using the Fisher exact test or unpaired Student's *t* test. Statistical calculations were performed using GraphPad

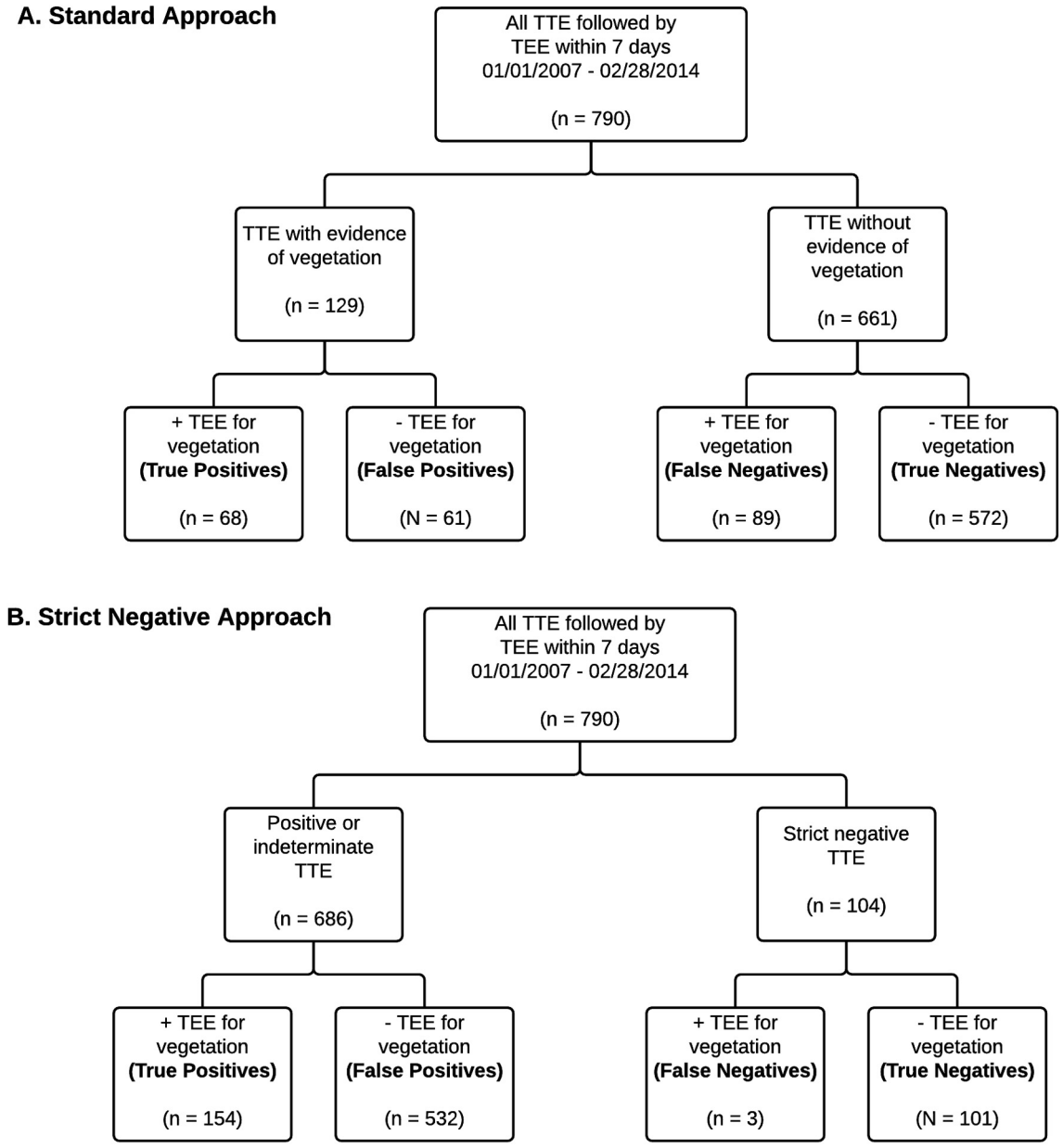

Figure 2 **(A)** Flow diagram showing the results of using the standard approach. **(B)** Flow diagram showing the results of using the strict negative approach.

(GraphPad Software, San Diego, CA), and *P* values $< .05$ were considered to indicate statistical significance. Results are presented as mean $\pm$ SD or values with 95% CIs.

Ethics

This study was performed using only information gathered as part of the routine clinical evaluation of patients at our institution and was carried out under approval of the Duke University School of Medicine Institutional Review Board.

RESULTS

Between January 1, 2007, and February 28, 2014, 3,495 transthoracic echocardiographic studies were performed to evaluate for IE. Of these, 790 studies met the inclusion criteria and were followed by TEE within 7 days. Among these 790 paired transthoracic and transesophageal examinations, 104 of the transthoracic studies met the strict criteria for negative results (13.2% of all included transthoracic studies) (Figure 1).

Baseline characteristics and blood culture data of the overall cohort, as well as the subgroup meeting the strict negative criteria, are shown in Table 1. The strict negative group was significantly younger, with lower rates of congestive heart failure, coronary artery disease, chronic kidney disease, and hypertension. The proportion of patients with positive blood cultures was similar in each group, as was the distribution of infectious organisms.

Using the standard approach, 661 of 790 transthoracic echocardiograms were read as negative for vegetation (no evidence of vegetation), and 129 were read as positive for vegetation (vegetation

Table 1 Baseline characteristics and blood culture data

Variable	Overall (*n* = 790)	Strict negative (*n* = 104)	Indeterminate/positive (*n* = 686)	*P*
Baseline characteristics				
Age (y)	57.3 ± 15.5	45.5 ± 13.6	59.2 ± 14.9	<.001
Women	335 (42%)	38 (37%)	297 (43%)	.20
Hypertension	599 (76%)	65 (63%)	534 (78%)	.001
Diabetes mellitus	366 (46%)	41 (39%)	325 (47%)	.14
Congestive heart failure	310 (39%)	9 (9%)	301 (44%)	<.001
Coronary artery disease	293 (37%)	8 (8%)	285 (42%)	<.001
Chronic kidney disease	372 (47%)	32 (31%)	340 (50%)	<.001
Renal dialysis status	169 (21%)	18 (17%)	151 (22%)	.31
COPD	51 (6%)	4 (4%)	47 (7%)	.29
Cerebrovascular disease	183 (23%)	12 (12%)	171 (25%)	.002
HIV positive	22 (3%)	7 (7%)	15 (2%)	.02
History of illicit drug abuse	48 (6%)	12 (12%)	36 (5%)	.02
Metastatic cancer	31 (4%)	4 (4%)	27 (4%)	1.00
Blood culture data				
Positive blood cultures	595 (75%)	85 (82%)	510 (74%)	.11
Species (% of positive cultures):				
S. aureus	157 (26%)	24 (28%)	133 (26%)	.69
Streptococcus spp.	28 (5%)	2 (2%)	26 (5%)	.41
Coagulase-negative *Staphylococcus*	61 (10%)	7 (8%)	54 (11%)	.70
Enterococcus	28 (5%)	1 (1%)	27 (5%)	.16
Polymicrobial, including *S. aureus*	209 (35%)	38 (44%)	171 (34%)	.05
Polymicrobial, excluding *S. aureus*	76 (13%)	5 (6%)	71 (14%)	.05
Other	36 (6%)	8 (9%)	28 (5%)	.21

COPD, Chronic obstructive pulmonary disease; *HIV*, human immunodeficiency virus.
Data are expressed as mean ± SD or as number (percentage). Note that statistical comparisons are between studies with strict negative results and those with indeterminate or positive results.

seen). Of the 661 transthoracic studies with negative findings, 89 had vegetations on subsequent TEE (Figure 2A). The resulting sensitivity of TTE using the standard approach was (68/157) = 43% (95% CI, 36%–51%), with an NPV of (572/661) = 87% (95% CI, 84%–89%) (Table 2).

The strict criteria, along with the number of transthoracic echocardiographic examinations not meeting each criterion, are listed in Table 3. Using these criteria, 104 transthoracic studies had negative results (meeting all of the strict negative criteria), and 686 had positive results (did not meet all of the strict negative criteria). Of the 104 patients meeting strict negative criteria, three had evidence of vegetation on subsequent TEE (Figure 2B). The resulting sensitivity of TTE using the strict negative approach was (154/157) = 98% (95% CI, 95%–99%), with an NPV of (101/104) = 97% (95% CI, 92%–99%) (Table 2).

By applying the calculated negative likelihood ratios listed in Table 2, the effect of negative results on TTE on posttest probability was estimated using each approach and is displayed as a test indication curve in Figure 3.

Among all 790 patients with TTE and TEE pairs, there was a 9.1% 30-day mortality rate and a 5.6% incidence of valve surgery within 180 days. The mortality and morbidity in the strict negative cohort were much less, with a 2.9% 30-day mortality rate and no patients undergoing valve surgery.

Table 2 Diagnostic characteristics of the standard approach and the strict negative approach

Variable	Standard approach (95% CI)	Strict negative approach (95% CI)
Sensitivity (%)	43.3 (35.8–51.1)	98.1 (94.5–99.3)
Specificity (%)	90.4 (87.8–92.4)	16.0 (13.3–19.0)
PPV (%)	52.7 (44.1–61.1)	22.4 (19.5–25.7)
NPV (%)	86.5 (83.7–88.9)	97.1 (91.9–99.0)
LR+	4.50 (3.34–6.06)	1.17 (1.12–1.22)
LR−	0.627 (0.546–0.721)	0.120 (0.038–0.373)

LR+, Positive likelihood ratio; *LR−*, negative likelihood ratio; *PPV*, positive predictive value.

Overall, 143 transesophageal echocardiographic studies (18.1%) were performed in the outpatient setting. Of these, 23 had positive results (23/143 = 16.1%), compared with 134 positive transesophageal studies among the inpatient group (134/647 = 20.7%) (*P* = .25). Of the 143 outpatient transesophageal studies, nine patients (6.2%) went on to valve surgery within 180 days, similar to the inpatient group (37/647 = 5.7%) (*P* = .84). The 30-day mortality rate among the 143 outpatient transesophageal studies was 4.9%,

Table 3 The strict negative criteria and number of transthoracic echocardiographic studies in the overall cohort not satisfying each criterion

Criterion	Number not meeting criterion
Moderate or better ultrasound quality	120 (15%)
Normal anatomy*	282 (36%)
No valvular stenosis or sclerosis	168 (21%)
Less than mild valvular regurgitation	478 (61%)
Less than moderate, simple pericardial effusion	6 (0.7%)
Absence of pacemaker/defibrillator leads, central venous catheter	164 (21%)
No evidence of vegetation	129 (16%)

*Normal anatomy defined as tricuspid aortic, pulmonic, and tricuspid valves, mitral valve without mitral annular calcification; no mitral valve prolapse; no atrial septal defect or ventricular septal defect, repaired or unrepaired.

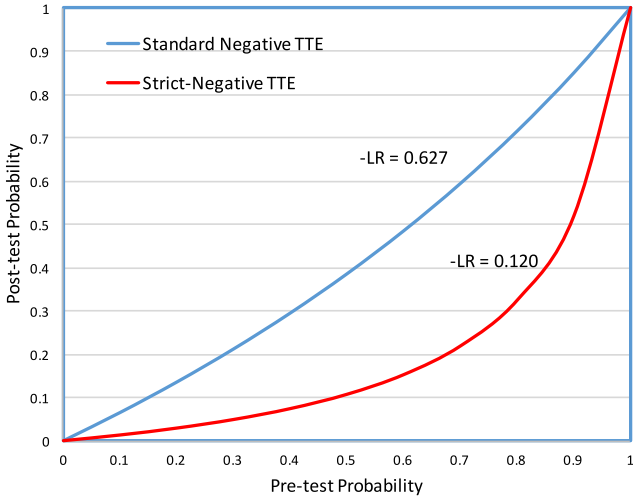

Figure 3 Test indication curve comparing the negative likelihood ratios for the standard and strict negative approaches. This figure uses the negative likelihood ratio to display the relationship between pre- and posttest probability for each approach. To focus on the improved NPV when using the strict negative criteria, the positive likelihood ratio curves were not included.

significantly less than the inpatient group (10.4%) ($P = .04$). Among the 104 transthoracic studies with negative results by the strict negative criteria, 22 patients (21.2%) underwent subsequent TEE as outpatients.

The clinical scenarios for the three patients with false-negative results on TTE by the strict criteria were reviewed. Patient A had a remote history of L4/L5 fusion and was found to have *Streptococcus mitis* bacteremia and osteomyelitis of his lumbar spine. TEE showed vegetation on the right coronary cusp of the aortic valve. Patient B was on chronic intravenous total-parenteral nutrition and was found to have subclavian thrombophlebitis and *Candida albicans* bacteremia. He had no central line at the time of TTE (it had been removed because of candidemia) and thus met our criteria for strict negative results on TTE. TEE showed a small mobile target on the aortic side of the right coronary cusp. Patient C had a history of intravenous drug abuse and was found to have pulmonary septic emboli and *Staphylococcus aureus* bacteremia. TEE showed a vegetation on the tricuspid valve. There was no evidence of abscess, fistula, or leaflet perforation on TEE and no IE-related mortality or surgery for these three patients.

DISCUSSION

In this large observational study, we compared two approaches for interpreting the results of TTE for IE as positive or negative. Using the standard approach, studies with evidence of vegetation on TTE were considered to have positive results, whereas all others were considered to have not positive results. Using the strict criteria approach, studies that fulfilled all strict criteria were considered to have negative results, and all other studies were considered to have not negative results (i.e., positive or indeterminate). The results of the study demonstrate that by using the strict negative criteria to define negative results on TTE for vegetation, the sensitivity and NPV of TTE for the presence of vegetation are greatly improved compared with the standard approach. This high sensitivity and NPV of the strict negative approach allows the identification of patients by TTE in whom subsequent TEE may not be needed to exclude vegetation.

These findings lend support to previous studies that have suggested that in the setting of *S. aureus* bacteremia, vegetation may be sufficiently excluded by negative findings on TTE in patients with low-risk features, such as an absence of intracardiac devices, embolic phenomena, prolonged bacteremia, prosthetic valves, hemodialysis, and secondary foci of infection.[28-34] The present study suggests that simple criteria based on transthoracic echocardiographic findings alone can be applied across a variety of infectious organisms. In contrast to prior investigators, we chose to examine the diagnostic characteristics of TTE in patients with native valves only.[35,36] In light of known ultrasound transmission limitations and echocardiographic artifacts associated with prosthetic valves, this approach is consistent with current guidelines for IE, in which initial TEE in patients with prosthetic valves is recommended.[2,3]

The overall cohort of patients in this study had an intermediate pretest probability for IE. TEE was performed in the outpatient setting for 18% of the overall cohort, and compared with those who underwent inpatient TEE, these patients had similar rates of vegetations and subsequent valve surgery but a lower mortality rate. The prevalence of cardiovascular and renal disease was high in the overall group, as was the number of patients with pacemaker or defibrillator leads or central venous catheters. Furthermore, all patients were believed to warrant TEE by their care providers at the time of evaluation, signifying greater clinical suspicion. The strict negative group had a lower prevalence of cardiovascular and renal disease but had a similar infectious organism distribution to the overall cohort, with *S. aureus* bacteremia representing the majority. Of note, 25% of the overall cohort did not have positive blood cultures recorded in our health system, which is likely due in large part to the high volume of referrals to our health center from outside institutions, at which cultures may have already been performed and antibiotics started.

Clinical Implications

The findings of this study suggest that in a patient with a low to intermediate pretest risk for endocarditis, TTE meeting the proposed strict

criteria can effectively rule out intracardiac vegetation. On the basis of the negative likelihood ratio of strict negative results on TTE, patients with pretest probability of up to 50% have a posttest probability of <10% (low risk) after strict negative findings on TTE. Compare this with the standard approach, with which patients with pretest probability of 50% and negative results on TTE still have a posttest probability of just under 40% (Figure 3). Although TEE is a safe and generally well-tolerated procedure, as an invasive procedure it is not without risk and cost.[37] Application of the proposed strict criteria for negative findings on TTE can identify a group of patients in whom vegetation is effectively excluded by TTE and who likely do not need the de facto follow-up TEE, standard in many practices.

It should be noted that in this study, we looked at the ability of TTE to rule out vegetation associated with IE compared with TEE, not the clinical diagnosis of IE. This approach is consistent with the methodology of prior work.[36,38] Also, the goal of this analysis was to identify patients in whom follow-up TEE might not add clinically relevant information. Although only 13.2% of all transthoracic echocardiographic studies met the strict negative criteria, these patients potentially represent a sizable population in whom the risk and costs of TEE can be avoided. Future work should evaluate the impact of each strict negative criterion on the sensitivity and NPV of negative results on TTE, as the ideal criteria would be maximally inclusive while maintaining strong sensitivity and NPV.

As described in the "Methods" section, our laboratory has a specific transthoracic echocardiographic image acquisition protocol for IE studies, which may affect the generalizability of our results. Through the use of fundamental frequencies and multiple zoomed views of valves, the protocol allows a careful examination for IE. It stands to reason that when TTE is performed in a less thorough fashion, its diagnostic value is reduced, and the incremental value of TEE is consequently increased. Attempting to use the strict criteria described in this study without focused valve imaging may thus affect the reproducibility of these results. We recognize that in many clinical laboratories, the time required to obtain multiple zoomed-in views on each valve and using both harmonic and fundamental frequency imaging may not seem feasible because of required laboratory throughput. However, as US health care shifts to a value-based rather than fee-for-service-based system, avoiding follow-up TEE in patients meeting strict negative criteria on endocarditis-protocoled TTE may prove to be economical in all practice settings.

Limitations

This large single-center retrospective study had several limitations. All echocardiographic data were based on the clinical reports stored in the DELD, without reviewing stored images, as clinical decision making was based on the initial clinical report. In the 7 years covered by this study, there were on average 24 accredited sonographers, and 10 Core Cardiovascular Training Statement level 3 readers per year, so although variability in image acquisition and interpretation was unavoidable, this study tested the strict negative criteria in a real-world academic setting with expert personnel.

Two of the three patients with transthoracic echocardiographic results meeting the strict negative criteria, but who went on to have positive results on TEE (false negatives), had high-risk features not accounted for by our study methods (patients B and C). Excluding these patients on the basis of a thorough chart review would have increased both the sensitivity and NPV of strict negative results on TTE to 99%. These cases also highlight that although echocardiography can provide valuable information to support the diagnosis of IE, it does not override clinical experience and judgment.

Limiting the studied population to patients with TTE followed by TEE within 7 days was necessary to test the diagnostic characteristics of TTE but likely introduced a posttest referral bias. Prior work has shown that posttest referral bias in settings in which initial "negative" test results lead to large numbers of patients not being referred to the definitive test can increase the apparent sensitivity and decrease the apparent specificity of the initial testing modality.[39] However, this bias should equally affect both the standard and strict negative criteria approaches, as both were applied to the same population of patients. Additionally, the standard practice at our institution is to perform follow-up TEE on any patient in whom suspicion of IE remains after initial TTE, so presumably patients with negative results on TTE and no follow-up TEE within 7 days were considered to have very low probability for IE. Our ability to assess the pretest probability of IE for the cohort was limited by the charted diagnoses available for each patient, and follow-up was limited to events occurring in our hospital system. Future studies testing strict negative criteria should be performed prospectively with accurate assessment of pretest probability and a standardized imaging and interpretation protocol for the study.

CONCLUSIONS

In patients undergoing evaluation for suspected IE, TTE has greatly improved sensitivity and NPV for vegetation when using strict criteria for negative results. In patients at low to intermediate risk with strict negative results on TTE, follow-up TEE may not be necessary to exclude vegetation.

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