

Role of Negative Trans-Thoracic Echocardiography in the Diagnosis of Infective Endocarditis

Marina Leitman MD, Eli Peleg MD, Ruthie Shmueli and Zvi Vered MD FACC FESC

Department of Cardiology, Assaf Harofeh Medical Center, Zerifin, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** The search for the presence of vegetations in patients with suspected infective endocarditis is a major indication for trans-esophageal echocardiographic (TEE) examinations. Advances in harmonic imaging and ongoing improvement in modern echocardiographic systems allow adequate quality of diagnostic images in most patients.

Objectives: To investigate whether TEE examinations are always necessary for the assessment of patients with suspected infective endocarditis.

Methods: During 2012–2014, 230 trans-thoracic echo (TTE) exams in patients with suspected infective endocarditis were performed at our center. Demographic, epidemiological, clinical and echocardiographic data were collected and analyzed, and the final clinical diagnosis and outcome were determined.

Results: Of 230 patients, 24 had definite infective endocarditis by clinical assessment. TEE examination was undertaken in 76 of the 230 patients based on the clinical decision of the attending physician. All TTE exams were classified as: (i) positive, i.e., vegetations present; (ii) clearly negative; or (iii) non-conclusive. Of the 92 with clearly negative TTE exams, 20 underwent TEE and all were negative. All clearly negative patients had native valves, adequate quality images, and in all 92 the final diagnosis was not infective endocarditis. Thus, the negative predictive value of a clearly negative TTE examination was 100%.

Conclusions: In patients with native cardiac valves referred for evaluation for infective endocarditis, an adequate quality TTE with clearly negative examination may be sufficient for the diagnosis.

IMAJ 2016; 18: 407–410

KEY WORDS: infective endocarditis (IE), trans-esophageal echocardiography (TEE), trans-thoracic echocardiography (TTE), vegetations, complications of endocarditis

Echocardiography is the foremost diagnostic modality for the accurate diagnosis of infective endocarditis. According to the Duke criteria, evidence of endocardial involvement is classified as a major diagnostic criterion for infective endocarditis and includes oscillating intracardiac masses on valves or supporting structures, in the path of regurgitant jets, or on

implanted material; or abscess formation, new dehiscence of prosthetic valve, or new valvular regurgitation [1]. Trans-esophageal echocardiography (TEE) is recommended in all cases when trans-thoracic echocardiography (TTE) is not diagnostic. With the development of modern echocardiographic systems, trans-thoracic ultrasonic imaging has improved significantly and allows high quality visualization of cardiac valves and valvular apparatus. Despite these improvements, cardiologists are often requested to perform TEE in all cases where infective endocarditis is suspected, regardless of TTE results or image quality. In this study we sought to investigate whether indeed TEE is always necessary in these patients.

PATIENTS AND METHODS

We searched the digital database of our echolab for echo exams that had been performed in patients with the clinical suspicion of infective endocarditis during 2012–2014. We found 230 such echo studies. Clinical and echocardiographic data of these patients were collected. Risk factors for infective endocarditis, microbiology data, co-morbidities, cardiac risk factors, and presence of prosthetic valves and intracardiac devices were all noted. Severe co-morbidities included malignant diseases, cognitive impairment, poor mobility, immune compromise, serious respiratory diseases, and chronic renal failure. Echo systems used in this study included Vivid 9 and Vivid i (General Electric, USA). Trans-thoracic echo exams were divided into three groups, based on the interpretation of the physician who signed the report:

- group 1: positive echo exams diagnostic for infective endocarditis
- group 2: patients with native valves and echo exams clearly negative for infective endocarditis
- group 3: non-conclusive exams in patients with inadequate echocardiographic window, and patients with prosthetic heart valves.

Subsequently, TEE examinations were performed based on clinical judgment. The outcome was determined based on data obtained from mortality records at the Ministry of the Interior. Final clinical diagnosis was available for all patients. Inter-observer variability was less than 5%.

STATISTICAL ANALYSIS

All data were expressed as mean value \pm standard deviation. Comparison between the patient groups was performed using Student's *t*-test for continuous data. In this study, *P* values $<$ 0.05 were considered significant. ANOVA (MATLAB) was used for multivariate analysis.

RESULTS

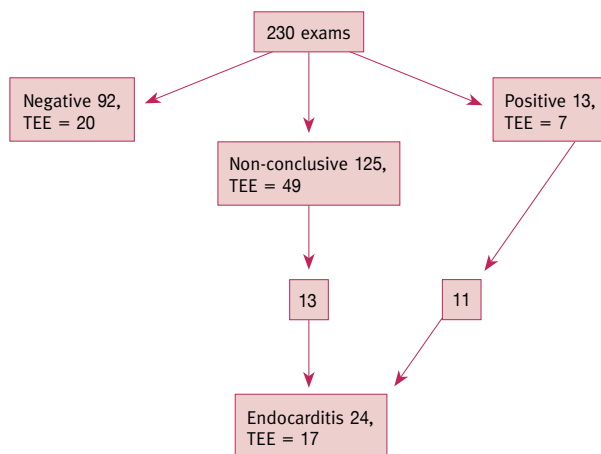
A total of 230 TTE exams were performed on 229 patients [Figure 1]. There were 122 (53%) men and 107 (47%) women, and the mean age was 64 ± 18 (range 20–93). Patients' characteristics are shown in Table 1. The most frequent indications for echocardiographic evaluation were fever, elevated C-reactive protein (CRP), and positive blood cultures. The most frequent infective agents were staphylococci, mostly methicillin-sensitive *Staphylococcus aureus* [Table 2]. TEE examination was performed in 76 patients (33%).

PATIENTS WITH INFECTIVE ENDOCARDITIS

Twenty-four (10%) patients had definite infective endocarditis, which was confirmed in 22 of them on echocardiography – TTE and/or TEE. In two patients vegetations were not visualized, and the diagnosis of infective endocarditis was clinical. Vegetations were found in 13 of 230 patients on TTE; in 2 of them small findings on the aortic valve were not confirmed on TEE and these patients were judged to be false positive. Among the remaining 11 trans-thoracic exams, TEE was done in 5 and was in agreement with TTE in all. In addition, in six patients with clear vegetations on TTE, TEE was not done.

In 11 of 13 patients with non-conclusive TTE exams vegetations were found on TEE. Most of the patients with definite endocarditis had positive blood cultures (22/24, 92%).

Figure 1. Classification of the patients into three groups



PATIENTS WITH CLEARLY NEGATIVE TTE [TABLE 3]

There were 92 patients with clearly negative TTE (group 2) and all had native valves. TEE was undertaken in 20 of them and no vegetations were found. In all these patients the final clinical diagnosis ruled out endocarditis, and an alternative source of

Table 1. Clinical features of the patients referred for echo to detect endocarditis

Age (years)	64 \pm 18
Male	122 (53%)
Female	107 (47%)
Diabetes	80 (35%)
Severe co-morbidities*	107 (47%)
Chronic renal failure	48(21%)
Vascular graft	7 (3%)
Permanent pacemaker	14 (6%)
Orthopedic devices	17 (7%)
Recent orthopedic surgery	20 (9%)
Prosthetic valve	9 (4%)
Post-valve repair	1 (0.4%)
Post-ASD closure	2 (0.9%)
Fever	203 (88%)
Elevated CRP reported	185 (80%)
Blood cultures	138 (60%)
TEE done	76 (33%)

*Severe co-morbidities: malignant diseases, cognitive impairment, poor mobility, immune compromised, serious respiratory diseases, chronic renal failure
ASD = atrial septal defect, CRP = C-reactive protein

Table 2. Infective agents

Any staphylococci	74
MSSA	39
MRSA	22
CONS	8
Enterococci	21
Any streptococci	21
<i>Candida</i>	10
Miscellaneous	26
<i>Klebsiella</i>	8
<i>Escherichia coli</i>	5
<i>Pseudomonas</i>	4
Other	9

MSSA = methicillin-sensitive *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*, CONS = coagulase-negative *Staphylococcus*

Table 3. Data of 92 patients with clearly negative TTE

	N	Died	Source of infection found	Blood cultures	CRP elevated	Fever	CRF	Severe co-morbidities	DM	Age	Staphylococci
TTE and TEE	20	6 (30%)	19 (95%)	17 (85%)	15 (75%)	15 (75%)	4 (20%)	14 (70%)	7 (35%)	58 ± 19	13 (18%)
TTE only	72	21 (29%)	72 (100%)	34 (47%)	52 (72%)	61 (85%)	11 (15%)	48 (67%)	21 (29%)	63 ± 13	12 (60%)
		NS	NS	$P < e^{-6}$	NS	NS	NS	NS	NS	NS	$P = 0.0001$

TTE = trans-thoracic echocardiography, TEE = trans-esophageal echocardiography, CRP = C-reactive protein, CRF= chronic renal failure, DM = diabetes mellitus

infection was found. Echocardiographic studies were performed between day 1 and 34 of admission (mean 7.5 ± 6.6 days). In the 20 patients in whom TEE was also performed there was no evidence of endocarditis. The patient who underwent TEE had positive blood cultures (85%) and staphylococci in blood cultures (60%) significantly more often.

The negative predictive value of negative TTE was calculated as: *patients with negative TTE and negative TEE (20) / patients with normal TTE and abnormal TEE (0) + patients with negative TTE and negative TEE (20) = 100%*.

Thus the negative predictive value of a negative TTE was 100%.

PATIENTS WITH NON-CONCLUSIVE ECHO EXAMS

Patients with non-conclusive echo exams were older than patients with definite echo results (68 vs. 60 years, $P < 0.001$), and there were more women than men (67/58 vs. 41/64, $P < 0.03$). These patients more often underwent TEE (49 vs. 27, $P < 0.03$) and more often had prosthetic valves (8 vs. 1, $P = 0.02$).

All patients with non-conclusive TTE exam had an inadequate echo window, which is crucial for definite diagnosis. Nine patients had prosthetic valves: three were biological and six were mechanical. TEE was performed in six of these patients; the other three did not undergo TEE based on the clinical judgment of the referring physician.

MULTIVARIATE ANALYSIS

A multivariate analysis was performed across all the 230 echo exams that were performed in search of infective endocarditis in 229 patients. Age ≥ 75 years independently predicted mortality risk of 50% during 1–3 years of follow-up ($P < e^{-5}$), chronic renal failure was associated with mortality risk of 51% ($P < 0.001$), and other severe co-morbidities were predictive of mortality in 41% ($P < e^{-6}$). Age ≥ 80 was associated with 53% risk of mortality ($P < 0.0001$). In association with positive blood cultures or severe co-morbidities, mortality was 58% ($P < 0.001$ and $P < 0.0001$ respectively). Positive blood cultures regardless of co-morbidities or age were associated with 36% risk of mortality ($P < 0.02$) in this study population.

DISCUSSION

The first echocardiographic experience with M-mode echo imaging of valvular vegetations was reported in 1973 [2]. Using

M-mode echo, vegetations were detected in 37%–69% [3,4]. Two-dimensional (2D) echocardiography improved visualization of vegetations [5] and complications of infective endocarditis [6]. In a study by Mugge et al [7], the detection rate of vegetations with older trans-thoracic 2D echocardiographic systems was 58%, whereas TEE detected vegetations in 90% [7]. In a later study, sensitivity of TTE for detection of vegetations among patients with positive blood cultures was 63%, and a main limiting factor of TTE examination was image quality [8]. Another study reported 55% sensitivity of TTE exams [9]. According to the latest guidelines, the sensitivity of TTE for diagnosing infective endocarditis on native valves is 50–90% [1]. In patients with a low clinical probability of infective endocarditis, even TTE examination, and certainly TEE, may be redundant [10,11]. The negative predictive value of a negative-normal TTE in the patients with possible native valve endocarditis in an earlier study was 90% [12]. One of the most recent studies also reported a large number of unnecessary TEE examinations, many of which could have been avoided [13]. In the large Italian registry of infective endocarditis for the period 2007–2010, echo exams were obtained on different echo systems with different image quality and in different hospitals. All the exams were classified as negative, uncertain, or positive. Sensitivity of TTE in the diagnosis of infective endocarditis in that study was 65% [14]. Recently, a practical algorithm was elaborated based on clinical risk stratification and normal TTE exam for the search of vegetations in patients with staphylococcal bacteremia [15].

Diagnostic workup in patients with endocarditis is essential in order to provide appropriate treatment. During recent years echocardiographic imaging has improved significantly. In the current single-center study we investigated a fairly large cohort referred for echocardiography with the clinical suspicion of infective endocarditis. The patients were managed based on the clinical decision of the responsible physician of each patient, and the final clinical diagnosis and patients’ outcome were assessed.

Patients can be managed in different ways: the specialist in infective disease will request TEE in every patient, the cardiologist will request it depending on TTE results and guidelines, and the physician on call will decide if cardiac search of infection is necessary based on the clinical setting [16].

Based on multivariate analysis, the patients referred for detection of vegetations are high risk patients. Performance of TEE in these patients may often be risky. In many cases there

is an alternative source of infection, which does not exclude infective endocarditis but may require prolonged extensive antibacterial treatment.

LIMITATIONS

Although all echo exams are stored in a digital format, our study is retrospective. Obviously, these observations should not be generalized to patients with prosthetic or heavily calcified native valves, or those with suboptimal TTE images. Complications of infective endocarditis, particularly abscess formation, valvular damage and perivalvular infection, are certainly better diagnosed by TEE. Nevertheless, our results indicate that TEE may not be necessary, at least initially, in carefully selected patients with fever, native valves and high quality clearly negative TTE, even those with positive blood cultures. In these selected patients the negative predictive value of TTE is very high.

CONCLUSIONS

In patients with native heart valves, who are referred for detection of vegetations and have clearly negative high quality trans-thoracic echocardiographic examination, TEE may not be necessary.

Correspondence

Dr. M. Leitman

Dept. of Cardiology, Assaf Harofeh Medical Center, Zerifin 70300, Israel

Phone: (972-8) 977-9736

Fax: (972-8) 977-8412

email: marina.leitman@gmail.com

References

- Nishimura RA, Otto CM, Bonow RO, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63 (22): 2438-88.
- Dillon JC, Feigenbaum H, Konecke LL, Davis RH, Chang S. Echocardiographic manifestations of valvular vegetations. *Am Heart J* 1973; 86 (5): 698-704.
- Come PC, Isaacs RE, Riley MF. Diagnostic accuracy of M-mode echocardiography in active infective endocarditis and prognostic implications of ultrasound-detectable vegetations. *Am Heart J* 1982; 103: 839-47.
- Roy P, Tajik AJ, Giuliani ER, Schattenberg TT, Gau GT, Frye RL. Spectrum of echocardiographic findings in bacterial endocarditis. *Circulation* 1976; 53 (3): 474-82.
- Wann LS, Hallam CC, Dillon JC, Weyman AE, Feigenbaum H. Comparison of M-mode and cross-sectional echocardiography in infective endocarditis. *Circulation* 1979; 60 (4): 728-33.
- Mintz GS, Kotler MN, Segal BL, Parry WR. Comparison of two-dimensional and M-mode echocardiography in the evaluation of patients with infective endocarditis. *Am J Cardiol* 1979; 43 (4): 738-44.
- Mügge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. *J Am Coll Cardiol* 1989; 14: 631-8.
- Erbel R, Rohmann S, Drexler M, et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by transesophageal approach. A prospective study. *Eur Heart J* 1988; 9 (1): 43-53.
- Reynolds HR, Jagen MA, Tunick PA, Kronzon I. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. *J Am Soc Echocardiogr* 2003; 16 (1): 67-70.
- Liu YW, Tsai WC, Hsu CH, et al. Judicious use of transthoracic echocardiography in infective endocarditis screening. *Can J Cardiol* 2009; 25 (12): 703-5.
- Greaves K, Mou D, Patel A, Celermajer DS. Clinical criteria and the appropriate use of transthoracic echocardiography for the exclusion of infective endocarditis. *Heart* 2003; 89: 273-5.
- McDermott BP, Cunha BA, Choi D, Cohen J, Hage J. Transthoracic echocardiography (TTE): sufficiently sensitive screening test for native valve infective endocarditis (IE). *Heart Lung* 2011; 40 (4): 358-60.
- Barton TL, Mottram PM, Stuart RL, Cameron JD, Moir S. Transthoracic echocardiography is still useful in the initial evaluation of patients with suspected infective endocarditis: evaluation of a large cohort at a tertiary referral center. *Mayo Clin Proc* 2014; 89 (6): 799-805.
- Cecchi E, Chirillo F, Faggiano P, et al. Italian Registry on Infective Endocarditis (RIE) Investigators. The diagnostic utility of transthoracic echocardiography for the diagnosis of infective endocarditis in the real world of the Italian Registry on Infective Endocarditis. *Echocardiography* 2013; 30 (8): 871-9.
- Showler A, Burry L, Bai AD, et al. Use of transthoracic echocardiography in the management of low-risk staphylococcus aureus bacteremia: results from a retrospective multicenter cohort study. *JACC Cardiovasc Imaging* 2015; 8 (8): 924-31.
- Kaasch AJ, Michels G. Staphylococcus aureus bloodstream infection: when is transthoracic echocardiography sufficient? *JACC Cardiovasc Imaging* 2015; 8 (8): 932-3.