Judicious use of transthoracic echocardiography in infective endocarditis screening

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BACKGROUND: Patients with a very low probability of infective endocarditis (IE) do not benefit from transthoracic echocardiography (TTE). Because the term 'very low probability' has not yet been defined, the present prospective study sought to identify the population with a 'very low probability'.

METHODS: TTE was performed between July 2005 and October 2006 in consecutive patients clinically suspected of having IE. Clinical parameters suggestive of IE and presence of infectious focus were recorded.

RESULTS: Twenty-four (15.5%) of 155 patients studied had positive findings on TTE. Significant positive predictors were embolic events, intravenous drug use, the presence of a prosthetic valve, positive blood cultures and immunological phenomena. The significant negative predictor was confirmed infection sites other than endocardium. Sixty-three (40.6%) of 155 patients without positive predictors were found to have no vegetation. Thus, the collective absence of these predictors indicated a zero probability of TTE showing evidence of IE. A significant negative predictor was a definite etiology of infection other than IE. Only one in 76 patients was diagnosed with both IE and infection at another site.

CONCLUSIONS: The absence of positive predictors or the presence of a negative predictor indicate a near-zero probability of IE being detected by TTE. Use of clinical parameters may avoid up to 41% of unnecessary TTE examinations, increasing the likelihood that such a diagnosis will be correct.

Key Words: Clinical predictors; Infective endocarditis; Transthoracic echocardiography

Diagnosis of infective endocarditis (IE) requires the interpretation of clinical, laboratory and echocardiography findings. Validations of the Duke criteria for diagnosis of IE have confirmed its high sensitivity and specificity, with emphasis on the role of echocardiography for both diagnosis and prognosis assessment because positive echocardiography evidence is a major criterion (1,2). Transthoracic echocardiography (TTE) for all patients suspected of having IE is both highly feasible and noninvasive (3), but its widespread use constitutes an unnecessary cost (4-6). American Heart Association guidelines (7) state that patients with 'a very low probability' of IE may not need TTE, but fail to define 'very low probability'. Few studies have addressed this issue using clinical parameters (8). Thus, the aim of the present prospective study was to identify the population with 'a very low probability' of IE.

METHODS

Subjects

One hundred fifty-five consecutive patients referred to the echocardiographic laboratory for TTE due to suspicion of IE were included in the

Usage judicieux de l'échocardiographie transthoracique dans le dépistage de l'endocardite infectieuse

HISTORIQUE : Les patients présentant une très faible probabilité d'endocardite infectieuse (EI) ne bénéficient pas de l'échocardiographie transthoracique (ÉCTT), parce que le terme « très faible probabilité » n'a pas encore été défini. L'étude prospective actuelle a tenté de circonscrire la population associée à une « très faible probabilité ».

MÉTHODES : Une ÉCTT a été effectuée entre juillet 2005 et octobre 2006 chez des patients consécutifs soupçonnés de souffrir d'EI sur la base de critères cliniques. Les paramètres évocateurs d'une EI et la présence d'un foyer infectieux ont été notés.

RÉSULTATS : Vingt-quatre patients (15,5 %) sur les 155 étudiés présentaient des signes positifs à l'ÉCTT. Les prédicteurs positifs significatifs ont été les complications emboliques, l'emploi de drogues intraveineuses, la présence d'une prothèse valvulaire, des hémocultures positives et un phénomène immunologique. Le principal prédicteur négatif a été la confirmation des foyers infectieux autres que l'endocarde. Soixante-trois patients sur les 155 (40,6 %) ne présentant pas de prédicteurs positifs se sont révélés indemnes de végétations. Ainsi, l'absence de l'ensemble de ces prédicteurs a indiqué une probabilité zéro de signes d'EI à l'ÉCTT. Un prédicteur négatif significatif a été une étiologie nette d'infection autre que l'EI. Un seul patient sur 76 a reçu un diagnostic d'EI et d'infection en un autre foyer.

CONCLUSIONS : L'absence de prédicteurs positifs ou la présence d'un prédicteur négatif indiquent une probabilité quasi nulle d'EI pouvant être détectée à l'ÉCTT. L'utilisation des paramètres cliniques permettrait d'éviter jusqu'à 41 % des examens par ÉCTT superflus, augmentant la probabilité que de tels diagnostics soient justes.

study. Diagnosis of IE was confirmed according to modified Duke criteria (1), rather than TTE or transesophageal echocardiography (TEE) findings. Predetermined clinical parameters (9) suggestive of or predisposed to IE were recorded by patient interview and review of medical records after obtaining informed consent. The predetermined clinical parameters were embolic events, immunological phenomena, current central venous access, any recent history of intravenous drug use, presence of a prosthetic heart valve, existence of a cardiac structural abnormality other than a prosthetic valve, positive blood culture and recurrent fever (38°C or higher for at least two days). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of the National Cheng Kung University Hospital (Tainan, Taiwan).

Echocardiography and image analysis

Standard TTE was performed on all patients by echocardiography specialists. All images were interpreted independently by two cardiologists unaware of any patient information. If the two reviewers disagreed, a

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TABLE 1
Clinical predictors in patients with and without evidence of infective endocarditis on transthoracic echocardiography (TTE)

Clinical predictors	TTE evidence of endocarditis			P
	Positive (n=24)	Negative (n=131)	Total (n=155)	
Embolic events	15 (62.5)	20 (15.2)	35 (22.6)	<0.0001
Immunological phenomena	11 (45.8)	15 (11.4)	26 (16.8)	<0.0001
Recurrent fever	22 (91.7)	106 (80.9)	128 (82.6)	0.201
Current central venous assessment*	5 (20.8)	35 (26.7)	38 (24.5)	0.62
Intravenous drug use*	9 (37.5)	4 (3.1)	13 (8.4)	<0.0001
Prosthetic heart valve*	3 (12.5)	1 (0.8)	4 (2.6)	0.012
Positive blood culture	23 (95.8)	46 (35.1)	69 (44.5)	<0.0001
Presence of cardiac structural abnormality (other than prosthetic valve)	8 (33.3)	42 (32.1)	50 (32.3)	0.903
Other infection focus*	1 (4.2)	75 (57.3)	76 (49.0)	<0.0001

Data presented as n (%). *Calculated by Fisher's exact test

TABLE 2
Sensitivity, specificity and predictive values of positive predictors for positive evidence of endocarditis on transthoracic echocardiography

Predictors	Sensitivity, Specificity,		PPV, %	NPV, %
	%	%		
Embolic events	59.3	85.2	45.7	90.8
Immunological phenomena	40.7	88.3	42.3	87.6
Intravenous drug use	33.3	96.9	69.2	87.3
Prosthetic heart valve	11.1	99.2	75.0	84.1
Positive blood culture	92.6	65.5	36.2	97.7

NPV Negative predictive value; PPV Positive predictive value

third cardiologist was asked to make the final decision. Images were acquired in the parasternal long- and short-axis views, and in apical two- and four-chamber views. All studies were performed using a phased array probe (range 1.6 MHz to 3.2 MHz; Sonos 7500, Philips Medical Systems, USA). The presence of vegetation was confirmed according to the major criteria of the modified Duke criteria: an oscillating mass on a valve or supporting structures, in the path of regurgitant jets, or on implanted materials without an alternative anatomical explanation; an abscess related to a prosthetic valve; new partial dehiscence of a prosthetic valve; and new valvular regurgitation (1). TEE was recommended and performed if clinical suspicion of endocarditis was high, but TTE findings were inconclusive.

Statistics

Sensitivity, specificity and predictive values were calculated according to standard definitions. The χ^2 or Fisher's exact tests were used for univariate analysis. $P < 0.05$ was considered to be statistically significant. All analyses were conducted using SPSS version 10.0 (SPSS Inc, USA).

RESULTS

One hundred fifty-five patients (mean $\pm$ SD) age 60 ± 14 years) were studied, of whom, 88 (56.7%) were men. Twenty-four patients (15.5%) had evident vegetation by TTE. Thirty (19.4%) of the 155 patients were referred for TEE to clarify the presence of vegetation due to poor image quality of TTE; 26 of these patients received TEE. Mechanical prosthetic valves produced many artefacts in the other four patients, making the presence of vegetation difficult to determine. Thus, these four patients also received TEE; vegetations were revealed in three cases.

TABLE 3
Number of positive predictors and proportion of positive transthoracic echocardiography (TTE) findings for infective endocarditis

Positive predictors, n	Patients in each group, n (%)	Patients with positive TTE, n (%)
0	63 (40.6)	0 (0)
1	56 (36.1)	5 (8.9)
2	21 (13.5)	5 (23.8)
3	11 (7.1)	10 (90.9)
4	4 (2.6)	4 (100)
5	0 (0)	0 (0)

Positive predictors are listed in Table 2

One patient was diagnosed as having IE by the Duke criteria, despite a negative TTE. He could not tolerate TEE due to his severe comorbid colon carcinoma (Dukes staging D). He received antibiotics for six weeks. The other 128 patients were followed to ensure no episodes of endocarditis occurred during their hospitalization.

Twenty-three patients presented with detectable vegetations on TTE examination, which was the only evidence of infection after close surveillance. *Streptococcus viridans* and *Staphylococcus aureus* were the most common causative pathogens.

The number of patients with each type of clinical parameter is presented in Table 1. Significant, independent parameters predictive of positive TTE findings included embolic events, intravenous drug use, presence of a prosthetic heart valve, positive blood cultures and immunological phenomena. A significant negative predictor was a definite etiology of infection other than IE. Of 76 patients with a definite infection other than IE, only one (with septic arthritis) was diagnosed as having IE, indicating that TTE for IE screening may not be necessary for patients with this condition.

The sensitivity, specificity and predictive values of a positive TTE for each parameter are shown in Table 2. Positive predictive values of these clinical parameters were not high, except for the presence of a prosthetic heart valve (75%) and intravenous drug use (69.2%), which accounted for a relatively small proportion of the total study population. On the other hand, all five positive predictors had high negative predictive values. Positive blood culture and presence of embolic events had the highest negative predictive values.

The numbers of positive predictors found in each patient and the corresponding rates of positive TTE findings are presented in Table 3. In a population with a high probability of IE (that is, with three or more positive predictors), the percentage of patients with positive TTE findings is more than 90%, while 63 patients (40.6%) with no positive predictors had negative TTE findings. Analysis indicated that the absence of positive predictors indicates a near-zero probability of vegetations on TTE. For patients with one or two positive predictors, rates of positive TTE findings were 8.9% and 23.8%, respectively.

DISCUSSION

In the present series of consecutively treated patients referred for TTE for suspicion of IE, criteria for 'very low probability' of IE were identified. Clinically significant parameters that might permit more judicious use of TTE in IE surveillance were identified. Positive predictors were embolic events, immunological phenomena, a recent intravenous drug abuse history, presence of a prosthetic valve and positive blood cultures. The collective absence of these five parameters indicated a near-zero probability of vegetations seen on TTE. The probability of positive TTE findings increased with the number of positive predictors presented, while the presence of a definite infection at a location other than the endocardial site was a significant negative predictor.

We recognize that endocarditis remains a clinical diagnosis that requires an in-depth understanding of epidemiology, predisposing factors, associated signs and symptoms, pathophysiology and organ system impact, as well as patient's risk characteristics (3). In spite of advances

in technology, echocardiography must not supplant clinical and microbiological diagnoses. The use of echocardiography in IE surveillance cannot be simplified because the problem is complex, and a missed diagnosis often results in significant morbidity and mortality (3). Therefore, the current European Society of Cardiology and American Heart Association guidelines (3,9) recommend that any patients suspected of having native valve endocarditis by clinical criteria should be screened by TTE. Furthermore, TTE is rapid and non-invasive, and has excellent specificity for vegetations (4,10). TTE is therefore widely used in IE surveillance. However, these results were influenced by the selection of patients in whom the diagnosis of IE was certain.

Although positive echocardiographic evidence has been included as a major criterion for IE diagnosis, the sensitivity of positively identifying vegetation by TTE is a moderate 40% to 80% (3-6). Technically, TTE views may be inadequate in up to 20% of adult patients due to obesity, chronic obstructive lung disease or chest wall abnormalities (3). Moreover, the rise in requests for echocardiography for IE evaluation have burdened both the health care system and echocardiographers, with little patient benefit. The American Heart Association guidelines suggested that the use of TTE is not indicated in patients with a very low probability of IE.

Few studies to date have attempted to identify the criteria that would define patients with 'a very low probability of IE'. In a retrospective study, Greaves et al (11) proposed the following criteria for performing TTE when IE is suspected: vasculitic or embolic phenomena, central venous access, recent history of intravenous drug use, presence of a prosthetic valve, and positive blood cultures. The presence of vasculitic or embolic phenomena had the highest positive (80%) and negative (98%) predictive values. All other criteria showed positive predictive values of less than 40% and negative predictive values of more than 92%. The proportion of patients with visible vegetations over valves and a positive finding on TTE, in the presence of one, two and three to five criteria were 14%, 40% and 46%, respectively (11). The positive clinical parameters of this study were not the same as those of our study and the positive rate of visible vegetations was much higher in our study. Furthermore, 48% of patients in the study by Greaves et al had none of the five criteria, and had no vegetation or other evidence of IE on TTE, indicating no probability of positive findings on TTE in the absence of clinical criteria.

Although many clinical predictors are well-known predisposing factors of IE – embolic events, immunological phenomena, intravenous drug use, prosthetic heart valves, positive blood culture, recurrent

fever, foreign bodies and structural heart disease – not all of them are significant enough predictors to permit more judicious use of TTE (eg, recurrent fever, foreign bodies, structural heart disease, etc) (9). Our study confirmed four of the five criteria set by Greaves et al and, most importantly, highlighted the criterion that may define the very low probability group: the collective absence of these five positive predictors.

Predictors in our study had relatively higher positive predictive values and lower negative predictive values than those of Greaves et al (11). The proportion of patients with positive TTE findings was lower when only one or two predictors were present, but reached 91% with three predictors present – much higher than the proportion noted by Greaves et al (46%). Moreover, we found a very reliable negative predictor: definite infection focus other than the endocardium. Among the 76 patients with other infection sources, one was hospitalized for septic arthritis, progressive multiorgan failure and vegetation on the tricuspid valve. TTE did not provide further information for the care of these patients, but added considerable cost. We also showed that the proportion of patients with positive TTE findings in the presence of only one positive predictor (9%) is still acceptable for TTE evaluation of IE. Therefore, we recommend TTE for patients with any single predictor established in the present study, in addition to the strong indication of TTE for patients with three or more positive predictors.

Limitations

Because the present study was performed in a single centre, patient selection may not be truly representative of the subject group at large. Moreover, IE may be present without evidence of vegetations on TTE (12). TEE, the more sensitive diagnostic tool, may be indicated for patients with high clinical suspicion of IE despite a 'negative' TTE study. As European Society of Cardiology guidelines (9) indicate, the semi-invasive nature of TEE and the need for operator expertise argue against its routine use in all patients with suspected IE. Indeed, fear of the discomfort of endoscopic examination caused a few patients to refuse TEE when IE was highly suspected.

CONCLUSION

Clinical predictors – positive or negative – may help guide health care professionals in their decision making regarding ordering TTE when IE is suspected. TTE may be unnecessary in the absence of the five positive predictors, or the presence of the negative predictor found in our study, thus preventing unnecessary use of TTE in cases with a very low probability of IE.

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