Transthoracic versus Transesophageal Echocardiography for Detection of Libman-Sacks Endocarditis: A Randomized Controlled Study

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ABSTRACT. ***Objective.*** Libman-Sacks endocarditis in patients with systemic lupus erythematosus (SLE) is complicated with thromboembolism, severe valve regurgitation, need for high-risk valve surgery, or death. Transesophageal echocardiography (TEE) is highly accurate for detection of valvular heart disease, but there are no prospective randomized controlled series comparing transthoracic echocardiography (TTE) to TEE for detection of Libman-Sacks endocarditis.

Methods. Eighty-one patients with SLE (73 women, 8 men) with a mean age of 39 ± 11 years and 75 healthy volunteers (40 women, 35 men) with a mean age of 35 ± 9 years underwent paired TTE and TEE to detect valve vegetations, thickening, or ≥ moderate mitral, tricuspid, or pulmonic ≥ mild aortic regurgitation. Paired TTE and TEE studies of patients and controls were randomized and interpreted by an experienced observer unaware of subjects' data.

Results. Libman-Sacks endocarditis: (1) was more common in patients than in controls by both TTE and TEE ($p < 0.001$); and (2) was more commonly detected by TEE than by TTE ($p \leq 0.05$); (3) TTE and TEE demonstrated poor agreement rates (kappa 0.02–0.54); and (4) considering TEE as the standard, TTE demonstrated a low sensitivity (63% overall, 11% for valve vegetations), low specificity (58%), low negative predictive value (40%), and a moderate positive predictive value (78%) for detection of Libman-Sacks endocarditis.

Conclusion. TEE is superior to TTE for detection of Libman-Sacks endocarditis and should be considered either as complement to a nondiagnostic TTE or as the initial test in patients with SLE with suspected cardioembolism, acute or subacute Libman-Sacks endocarditis with moderate or worse valve dysfunction, or superimposed infective endocarditis. (First Release Dec 15 2007; J Rheumatol 2008;35:224–9)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
LIBMAN-SACKS ENDOCARDITIS
TRANSESOPHAGEAL ECHOCARDIOGRAPHY
VALVULAR HEART DISEASE
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DIAGNOSTIC ACCURACY

Libman-Sacks endocarditis in patients with systemic lupus erythematosus (SLE) is highly prevalent; manifests as valve vegetations, thickening, regurgitation, or rarely stenosis; and is complicated with thromboembolism, noninfective and infective valvulitis, severe valve regurgitation, the need for high-risk valve surgery, or death[1-6]. Accurate detection of Libman-Sacks endocarditis may lead to therapy that may prevent the occurrence or recurrence of these complications. Most clinicians utilize transthoracic echocardiography (TTE) for the evaluation of Libman-Sacks endocarditis despite the fact that transesophageal echocardiography (TEE) is a more accurate method for detection of valvular heart disease and valve masses[7]. Our study directly addresses this question using a prospective randomized controlled design comparing TTE to TEE for detection of Libman-Sacks endocarditis.

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MATERIALS AND METHODS

Study design and populations. This was a prospective randomized controlled study conducted at the University of New Mexico and Veterans Affairs Health Sciences Centers. Eighty-one patients (73 women, 8 men) with diagnosis of SLE, 67 (83%) outpatients and 14 (17%) inpatients, with a mean age of 39 ± 11 years (range 16–62), and a disease duration of 12 ± 13 years (range 1-29) agreed to participate. Patients were recruited as they were encountered in clinic or hospital wards and therefore they represent the typical patients with SLE seen in clinical practice with a broad spectrum of clinical, laboratory, and therapy characteristics. We excluded patients with prosthetic valves, history of or suspected infective endocarditis, history or documented non-SLE related valvular heart disease, and those < 18 and > 65 years old. Also, 75 healthy volunteers (40 women, 35 men) with a mean age of 35 ± 9 years (range 17–57) were recruited among medical, paramedical, or general personnel of the participating medical centers. The design was a paired and prospective

randomized series where each subject with SLE and control had both TTE and TEE.

Echocardiography. All subjects with SLE underwent TTE immediately before or after TEE in 88% and within a month of each other in 12%. All controls underwent both studies within 24 hours. TTE and TEE studies were separately videotaped or digitally acquired for offline interpretation. Standard 2-dimensional (2-D) views were obtained at a depth of 8–12 cm (for TTE) and at 4-6 cm (for TEE) with a narrow sector scan to improve image resolution of the heart valves. Electronic calipers were used to determine the thickness of valve leaflets and size of valve vegetations using M-mode and 2-D images, respectively. Color, pulsed, and continuous-wave Doppler recordings were obtained to assess valve regurgitation or stenosis.

Criteria for interpretation. Valve vegetations were defined by TTE and TEE as abnormal localized echodensities with well defined borders as part of or adjacent to the valve leaflets or annulus, or subvalvular apparatus. Valve thickening: normal thickness of the atrioventricular and semilunar valves by TEE ranges from 0.7 to 3 mm and 0.7 to 2 mm, respectively[8]. Therefore, abnormal valve thickening by TEE was considered present when a thickness > 3 mm (for mitral and tricuspid valves) or > 2 mm (for aortic and pulmonic valves) was demonstrated. Valve thickening by TTE was visually assessed. Valve regurgitation was graded as mild, moderate, moderate to severe, or severe. Jet area, jet area to atrial area ratio, and width of the vena contracta by color-Doppler and intensity of the continuous-wave Doppler signal were used for assessing mitral and tricuspid regurgitation. Jet width, jet height to ventricular outflow-tract height ratio, and width of the vena contracta by color Doppler, and pressure half time by continuous-wave Doppler were used for assessing aortic and pulmonic regurgitation[9]. Thus, Libman-Sacks endocarditis was defined as valve vegetations, valve thickening, or ≥ moderate mitral, tricuspid or pulmonic or ≥ mild aortic regurgitation. To validate the interpretation of echocardiograms, TTE and TEE studies of patients were randomly intermixed with those of controls and were interpreted by an experienced observer unaware of subjects' clinical data.

Rationale for assessment of the diagnostic value of TTE using TEE as the standard. The ideal assessment of the diagnostic value of TTE and TEE for detection of Libman-Sacks endocarditis would be a direct comparison with surgical or postmortem findings. However, a surgical or pathologic standard is difficult to achieve for several reasons: (1) Libman-Sacks endocarditis is predominantly subclinical; (2) thus, most patients with Libman-Sacks endocarditis do not require valve surgery or die; (3) patients who do undergo valve surgery are those with the worst degree of disease likely to be detected by both techniques; (4) patients who die do not always undergo postmortem evaluation; and (5) a control group is not feasible. In this study, TEE was used as a surrogate measure for anatomic valve pathology since findings of valvular heart disease on TEE correlate highly with those of surgical and postmortem pathology[7,10,11].

Statistical analysis. The frequencies of valve abnormalities were determined by TTE and TEE among patients and controls. Kappa coefficients were used to determine chance-adjusted rates of agreement between TTE and TEE for detection of valve abnormalities. McNemar's test was used to assess marginal homogeneity for the paired comparison of categorical variables between techniques. Fisher's exact test was used for comparison of categorical variables between groups. The sensitivity, specificity, and predictive values of TTE for detection of valve abnormalities were determined using TEE as the standard. Finally, percentage agreement rates were used to determine interobserver variability in detecting valve abnormalities by TEE and TTE separately. A 2-tailed $p < 0.05$ was considered significant.

RESULTS

Frequency, distribution of types, and rates of agreement for valve abnormalities by TTE and TEE in patients and controls. By both TTE and TEE, each and any valve abnormality was significantly more common in patients with SLE than in controls ($p < 0.001$ for all). In SLE, valve vegetations, valve thickening, ≥ mild aortic regurgitation, and any valve abnormality were significantly less common by TTE than by TEE (6%, 52%, 6%, and 57% vs 46%, 70%, 14%, and 70%, respectively; $p \leq 0.05$ for all) (Table 1). Consequently, the rate of agreement between TTE and TEE for detection of these valve abnormalities was poor (0.02–0.54) due primarily to low sensitivity of TTE compared to TEE. In healthy controls, the frequency of valve abnormalities was low and similarly detected by TTE and TEE.

Diagnostic value of TTE using TEE as the standard. Valve vegetations: for detection of any valve, mitral valve, and aortic valve vegetations, TTE demonstrated a very low sensitivity (11%, 8%, and 12%, respectively) and a low to moderate negative predictive value (57%, 71%, and 81%, respectively; Table 2, figure 1). The overall high specificity and positive predictive value of TTE for detection of valve vegetations (98% and 80%) are seriously undermined as useful diagnostic measures due to its low detection rate (low sensitivity) of vegetations. Valve thickening: for detection of any valve, mitral valve, and aortic valve thickening, TTE also demonstrated a low sensitivity (53%, 57%, and 39%) and a low to moderate negative predictive value (31%, 58%, and 67%), specificity (50%, 63%, and 87%), and positive predictive value (71%, 57%, and 68%). Valve regurgitation: for detection of any valve regurgitation, ≥ moderate mitral regurgitation, and ≥ mild aortic regurgitation, TTE demonstrated a low sensitivity (54%, 57%, and 36%), a high negative predictive value and high specificity, and a moderate to high positive predictive value.

Interobserver agreement rates for detection of valvular heart disease by TEE and TTE. Forty-five randomly selected TEE studies (from 37 patients and 8 controls) were independently interpreted by 2 experienced observers. The percentage agreement rates for detection of mitral and aortic valve vegetations, thickening, and regurgitation were 96% and 98%, 93% and 87%, and 98% and 93%, respectively[1]. Also, 36 randomly selected TTE studies (18 patients and 18 controls) were independently interpreted by the same 2 observers. The percentage agreement rates for detection of mitral and aortic valve vegetations, thickening, and regurgitation were 97% and 100%, 72% and 86%, and 100% and 100%, respectively.

DISCUSSION

There are 5 major findings in our study: (1) valvular heart disease is significantly more common in patients with SLE than in controls ($p < 0.001$ for all valve abnormalities); (2) TEE detected Libman-Sacks endocarditis more commonly than TTE, especially valve vegetations; (3) TTE and TEE demonstrated poor inter-method agreement for detection of Libman-Sacks endocarditis (kappa 0.02–0.54); (4) using TEE as the standard, TTE demonstrated an overall low sensitivity (63% overall, 11% for valve vegetations), low specificity (58%), low negative predictive value (40%), and a moderate positive predictive value (78%) for detection of Libman-Sacks endo-

Table 1. Comparison of transthoracic (TTE) and transesophageal echocardiography (TEE) for detection of valvular heart disease in patients and controls.

Abnormality	Patients, n = 81				Controls, n = 75			
	TTE, n (%)	TEE, n (%)	p	Kappa	TTE, n (%)	TEE, n (%)	p	Kappa
Vegetations	5 (6)	37 (46)	< 0.001	0.09	0	2 (3)	0.50	
Mitral valve	2 (2.5)	25 (31)	< 0.001	0.11	0	1 (1.3)	1.0	
Aortic valve	2 (2.5)	17 (21)	< 0.001	0.17	0	1 (1.3)	1.0	
Thickening	42 (52)	57 (70)	0.02	0.02	12 (16)	8 (11)	0.29	0.20
Mitral valve	35/80* (44)	39/80 (49)	0.49	0.15	10/72 (14)	5/72 (7)	0.13	0.19
Aortic valve	19/80 (24)	33/80 (41)	0.006	0.28	4/71 (6)	3/71 (4)	0.56	0.55
Regurgitation†	19 (23)	24 (30)	0.23	0.46	2 (3)	3 (4)	0.56	0.38
≥ Moderate MR	12/80 (15)	14/80 (18)	0.53	0.54	0	0		
≥ Moderate TR	5/80 (6)	3/80 (4)	0.32	0.48	1/71 (1.4)	0		
≥ Mild AR	5/80 (6)	11/80 (14)	0.03	0.45	1/71 (1.4)	3/71 (4)	0.16	0.49
Any abnormality††	46 (57)	57 (70)	0.05	0.19	13 (17)	8 (11)	0.23	0.07

Blank entries for p and Kappa represent rates too small for statistical comparison. * Denominator is shown when different from total number of patients or controls. † Includes ≥ moderate mitral, tricuspid, or pulmonic or ≥ mild aortic regurgitation. †† Includes valve vegetations, valve thickening, or ≥ moderate mitral, tricuspid or pulmonic or ≥ mild aortic regurgitation. MR, AR, TR: mitral, aortic, and tricuspid regurgitation, respectively.

Table 2. Diagnostic value of transthoracic echocardiography for detection of Libman-Sacks endocarditis using transesophageal echocardiography as the standard.

Valve Abnormality	Sensitivity, n (%)	Specificity, n (%)	Positive Predictive Value, n (%)	Negative Predictive Value, n (%)
Vegetations	4/37 (11)	43/44 (98)	4/5 (80)	43/76 (57)
Mitral valve	2/25 (8)	56/56 (100)	2/2 (100)	56/79 (71)
Aortic valve	2/17 (12)	64/64 (100)	2/2 (100)	64/79 (81)
Thickening	30/57 (53)	12/24 (50)	30/42 (71)	12/39 (31)
Mitral valve	20/39 (57)	26/41 (63)	20/35 (57)	26/45 (58)
Aortic valve	13/33 (39)	41/47 (87)	13/19 (68)	41/61 (67)
Regurgitation	13/24 (54)	51/57 (89)	13/19 (68)	51/62 (82)
≥ Moderate MR	8/14 (57)	62/66 (94)	8/12 (78)	62/68 (91)
≥ Mild AR	4/11 (36)	68/69 (99)	4/5 (80)	68/75 (91)
Any	36/57 (63)	14/24 (58)	36/46 (78)	14/35 (40)

Abbreviations as in Table 1.

carditis; and finally (5), a high specificity of TEE in the evaluation of Libman-Sacks endocarditis based on the low level of detection of valve abnormalities in controls. The cross-sectional recruitment, the randomized paired TTE-TEE design, the use of both a normal control group and each subject as his own control, admixing of studies and blinding of interpretation, and high interobserver agreement rates by TEE and TTE for detecting valve abnormalities validate the statistical analyses and clinical utility of our data.

Accurate detection of Libman-Sacks endocarditis, especially of valve vegetations, is of significant clinical relevance for several reasons. In a general population, the proportion of cardioembolic strokes is 20% and is higher for transient ischemic attacks (TIA). In patients with SLE with a high prevalence of Libman-Sacks endocarditis and hypercoagulability, the incidence and recurrence of stroke and TIA are higher and are associated with significant morbidity and mortality[3,12,13]. In a recent series, 37 patients with SLE underwent clinical evaluation, magnetic resonance imaging (MRI) of the brain, and TEE[3]. Stroke, TIA, or cerebral infarcts occurred in 19 patients (51%) and left-sided valvular heart disease was detected in 25 patients (68%). Any valvular heart disease and lupus anticoagulant antibody were the only independent predictors of cerebrovascular disease [odd ratios (OR) 5.3 to 10.6, all $p < 0.03$]. Mitral valve thickening was the only independent predictor of stroke or TIA (OR 10.4, $p = 0.02$). In a subset of 28 patients with SLE, 18 (64%) had cognitive dysfunction, acute confusion, seizures, or psychosis[14]. Valve vegetations by TEE were more common in patients with than in those without neurological dysfunction, and in those with old cerebral infarcts (61% vs 10% and 75% vs 30%, respectively; $p \leq 0.02$ for both), and were strong independent predictors of nonfocal neurologic dysfunction (OR 16.5, $p = 0.03$]. Several series using TTE have also demonstrated an association of valve thickening or regurgitation [vegetations are infrequently detected (= 10%) by this technique] with cerebrovascular

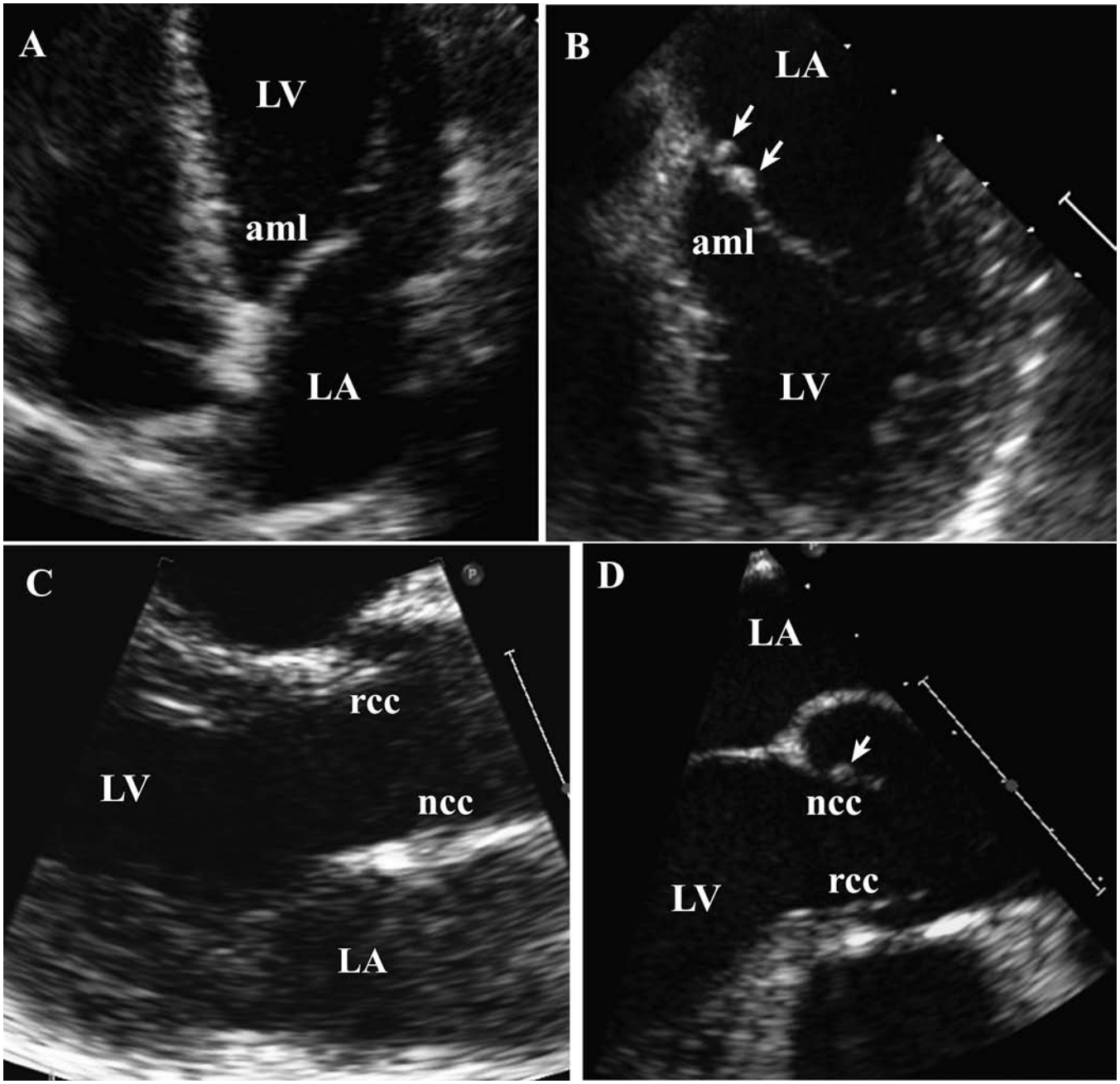

Figure 1. Detection of Libman-Sacks endocarditis by transthoracic and transesophageal echocardiography. A. TTE 4-chamber view in a young patient with SLE and a recent transient ischemic attack shows diffuse thickening of the anterior mitral leaflet (aml), but no vegetations. B. In contrast to (A), this TEE 4-chamber view shows normal thickness of the aml, but 2 small sessile vegetations located at the base and atrial side of the aml (arrows). Associated mild mitral regurgitation was shown by both techniques. C. This TTE parasternal long-axis view in an asymptomatic young patient with SLE shows mild thickening of the aortic right coronary cusp (rcc) and a normal appearing noncoronary cusp (ncc). D. In contrast to (C), this TEE view longitudinal to the left ventricular outflow tract shows a normal-appearing aortic rcc, but an abnormal ncc with a small vegetation located in the mid-portion and aortic side of the cusp (arrow), with associated mild thickening. Neither technique demonstrated aortic regurgitation. The different location of the aortic valve cusps is due to the anteroposterior imaging plane by TTE and posteroanterior imaging plane by TEE. LA: left atrium, LV: left ventricle.

disease. In a series using TTE in 69 patients with SLE, valve thickening was 30% significantly more common in patients with than in those without cerebral infarcts, white matter abnormalities, punctate lesions, or any focal brain lesion on MRI ($p \leq 0.05$ for all)[15]. In a series of 71 patients with SLE, valvular heart disease was an independent predictor of stroke or TIA[16]. In another series of 113 patients with antiphospholipid syndrome (38% of them with SLE), valvular heart disease was more common in those with than in those without stroke (38% vs 13%; $p = 0.01$)[17]. Recent series using trans-

cranial Doppler for detection of cerebral microemboli further support a causal association of Libman-Sacks endocarditis with cerebrovascular disease[18,19]. In addition, in fatal cases of lupus cerebrovascular disease, about two-thirds of patients have multiple cerebral cortical microinfarcts characterized by fibrin or platelet thrombi deposition in the small blood vessels, and 15% to 20% have cerebral infarcts without vascular obstruction suggestive of transient thrombosis[20,21]. In contrast, cerebral vasculitis, atherosclerosis, and cerebritis are rare (< 1%) in these series. All these TEE and TTE series support that Libman-Sacks endocarditis with valve vegetations or perhaps valve thickening is a source of fibrin or platelet macro- or microembolism leading to ischemic brain injury and focal or nonfocal neurological dysfunction. Thus, in patients with SLE with focal or nonfocal central nervous system disease a TEE and infrequently a TTE demonstrating valve vegetations define a likely embolic cause of cerebral dysfunction, and support the use of anticoagulant and/or antiinflammatory therapy. A negative TEE would direct the search of a hypercoagulable state, vasculitis, cerebritis, atherosclerosis, or drug or metabolic effects. In contrast, a negative or positive TTE with valve thickening, but no valve vegetations, would not exclude or establish a causal association and would make the use of anticoagulation debatable. A prospective randomized and controlled cross-sectional and longitudinal study is needed to determine the incidence of cerebrovascular disease and the influence of antiplatelet or anticoagulant therapy on its primary or secondary prevention in patients with SLE and valve thickening or regurgitation, but no vegetations on TTE or TEE.

As a result of recurrent valvulitis and/or thrombosis, patients with SLE with valve thickening and moderate valve dysfunction have a 3- to 4-fold higher rate of progression to symptomatic valvular heart disease, need for valve surgery, and death over a 2–8 year followup as compared to those without or those with mild valvular disease[1,4,22]. Because of their immunosuppressed state and multisystem disease, valve replacement in lupus patients poses up to 25% mortality as compared to 3% in the general population. Thus, an accurate and early detection of Libman-Sacks endocarditis requiring antiinflammatory, antiplatelet, or anticoagulant therapy may prevent progression of the disease.

Infective endocarditis is a well-known superimposed complication of active or healed Libman-Sacks endocarditis. Also, infective endocarditis can mimic or trigger a flare of SLE and if unrecognized can rapidly lead to severe valve dysfunction, heart failure, and septic death[5,23]. Further, a flare of SLE can mimic infective endocarditis (pseudoinfective endocarditis). A low white blood cell count, elevated antiphospholipid antibodies, negative or low C-reactive protein, negative blood cultures, and typical echocardiographic, especially TEE findings, support the diagnosis of Libman-Sacks endocarditis[1,3,24,25].

Therefore, based on the results of this and other series and according to recently published appropriateness criteria for echocardiography in a general population[26], TEE should be considered either as complement to a nondiagnostic TTE or as the initial test in patients with SLE with suspected cardioembolism, acute or subacute Libman-Sacks endocarditis with moderate or worse valve dysfunction, or superimposed infective endocarditis. In patients with stable SLE with a heart murmur or in those with known valvular dysfunction (regurgitation and/or stenosis) without a change in clinical status, TTE is appropriate as the initial and followup diagnostic method (Table 3).

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Table 3. Appropriateness criteria for echocardiography in native valvular heart disease in a general population and applicable to patients with SLE.

Use of TEE as the initial test — common uses	Score*
1. Evaluation for cardiovascular source of embolic event in a patient who has normal TTE and normal ECG and no history of atrial fibrillation/flutter	U (6)
2. To determine mechanism of regurgitation and determine suitability of repair	A (9)
3. To diagnose/manage endocarditis with a moderate or high pretest probability (e.g., bactermia, especially Staph. bacteremia or fungemia)	A (9)
Use of TTE as the initial test — common uses	
1. Initial evaluation of murmur in patients for whom there is a reasonable suspicion of valvular or structural heart disease	A (9)
2. Initial evaluation of known or suspected native valvular regurgitation	A (9)
3. Routine (yearly) evaluation of an asymptomatic patient with severe native valvular regurgitation with no change in clinical status	A (8)
4. Reevaluation of native valvular regurgitation in patient with a change in clinical status	A (9)
5. Initial evaluation of suspected native infective endocarditis with positive blood cultures or a new murmur	A (9)
6. Initial evaluation for cardiovascular source of embolic event (PFO/ASD, thrombus, neoplasm)	A (8)
7. Initial evaluation of cardiac mass (suspected tumor or thrombus)	A (9)

TEE: transesophageal echocardiography; A: appropriate; U: uncertain; PFO: patent foramen ovale; ASD: atrial septal defect; SLE: systemic lupus erythematosus. Other abbreviations as in Table 1. * An appropriateness score of 7–9 indicates that the test is generally acceptable and is a reasonable approach for the indication. A score of 4–6 indicates that the test may be generally acceptable, and may be a reasonable approach for the indication, and more research and/or patient information is needed to classify the indication definitively (Adapted with permission from Douglas, et al. J Am Soc Echocardiogr 2007; 21:787–805[26]).

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