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Echocardiography in the Assessment of Patients with Rheumatologic Diseases

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Abstract Cardiovascular disease is an important extra-articular manifestation of rheumatologic diseases leading to considerable mortality and morbidity. Echocardiography emerges as a useful non-invasive technique for the screening and evaluation of cardiac involvement in these patients. With the technological advancement in echocardiographic techniques, we have gained a greater appreciation of the prevalence and nature of the cardiac involvement in these patients, as detection of subclinical disease is increasingly feasible. This review discusses cardiac involvement in patients with rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, systemic sclerosis and ankylosing spondylitis, and the role of different echocardiographic modalities in their evaluation.

Keywords Echocardiography · Cardiac disease · Ischaemia · Left ventricular function · Rheumatologic diseases · Connective tissue disease

This article is part of the Topical Collection on *Echocardiography*

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Introduction

Rheumatologic diseases are autoimmune inflammatory disorders that include, among others, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APAS), systemic sclerosis (SS) and ankylosing spondylitis (AS). These disorders affect various anatomic structures within the heart, leading to a wide array of cardiac manifestations that may be clinically silent or cause considerable morbidity and mortality [1•]. Cardiac involvement can be due to multiple mechanisms—including immunologic abnormalities, inflammation, small vessel disease, accelerated atherosclerosis and increased coagulability [2]. The cardiac manifestations of these conditions vary widely in terms of prevalence and severity (Table 1).

Echocardiography is the most useful non-invasive technique for the evaluation of cardiac involvement in patients with rheumatologic diseases [23]. Data from studies on the prevalence of cardiovascular (CV) involvement have not been consistent due to variabilities in the detection methods (diagnostic sensitivities of different echocardiographic techniques, type of cardiac abnormalities, diagnostic criteria and frequency of examinations), patient-related factors (age, disease severity, chronicity, duration of follow-up and background therapy) and lack of a gold standard for confirmation of observed abnormalities [24, 25]. Additionally, the diagnostic capability of novel echocardiographic modalities has allowed the detection of early subclinical cardiac involvement such as diastolic dysfunction and coronary microvascular dysfunction (CMD).

Table 1 Cardiovascular manifestations of rheumatologic diseases

	Systolic dysfunction	Diastolic dysfunction	Ischaemia	Valve disease	Pulmonary hypertension
Rheumatoid arthritis	-3× increased risk of LVSD compared to controls. Potential aetiologies include: -Myocarditis: Focal non-specific, diffuse necrotizing or granulomatous. -Drug-related cardiomyopathy (corticosteroids and anti-malarials). -Ischaemic heart disease. -End-stage amyloidosis [3].	-Present in up to 76 % of patients compared to 49 % of controls. Impaired relaxation in 65 %, pseudonormal in 25 % and restrictive filling pattern in 10 % [4].	-Associated with a 2–3× increased risk of MI with standardized cardiovascular mortality ratio of 1.5 compared with the general population [5••]. -Ischaemia may be caused by premature epicardial CAD and/or CMD [5••].	-Includes thickening, regurgitation and rheumatoid nodules. Valve abnormalities are reported in 47 % on 2D-TTE [6] and 59 % of patients on 2D-TEE, commonly involves the mitral valve followed by the aortic [7].	-Present in 8–12 % [8].
Systemic lupus erhythemat-osus	-LVEF ≤ 50 % is reported in 2.8 % [9]. -Potential aetiologies for LVSD include: -Lupus autoimmune myocarditis (more commonly subclinical) [10]. -Cardiomyopathy: HTN and ischaemic (more common) and hydroxychloroquine related. -Ischaemic heart disease [10].	-Present in up to 72 % of patients. Main findings on echocardiography include prolonged isovolumetric relaxation time and lower *E*/*A* and *E*′/*A*′ ratios [9]	-Premature epicardial CAD results from inflammation, traditional CAD risk factors and drug side effects [11]. -Associated with a 5–6× increased risk of CV events compared to the general population. 50× increase in risk of MI among women aged 35–44 years and standardized cardiovascular mortality ratio of 2.72 [5••]. -Ischaemia may also result from arteritis, vasospasm, coronary thrombosis, embolization and CMD [10].	-Present in 41–73 % on TEE and includes thickening, Libman–Sacks vegetations, regurgitation and, rarely, stenosis. Valve regurgitation may become severe in 12 % on long-term follow-up.	-Present in 6 % [12].
Anti-phospholip-id antibody syndrome	-May be due to direct effect of immune complex or ischaemia caused by coronary macro- or microvascular thrombosis [13•]	-Diastolic dysfunction reported but prevalence is unclear	-Ischaemia caused by coronary thrombosis, embolism, accelerated atherosclerosis or CMD. Coronary embolism is the most frequent aetiology in young patients [13•, 14].	-Present in 32–38 % of the patients on TTE and includes leaflet thickening, vegetations, non-bacterial thrombotic endocarditis, mitral regurgitation and, rarely, stenosis [13•]. Functional and structural valvular abnormalities present in 87 % on TEE [15]	
Systemic sclerosis	-LVEF < 55 % is reported in 7 % of patients. -Myocardial fibrosis in a "mosaic", "patchy" distribution. Foci of contraction band necrosis may also occur. The fibrotic areas do not correlate with coronary distribution [16]. - Reversible vasospastic abnormalities and fixed vascular abnormalities due to fibrosis or organic abnormalities of small coronary vessels contributed to myocardial dysfunction [17].	-Present in 17.4–55 % of the patients [16, 18].	-Premature epicardial CAD less frequent than in RA and SLE [16]. -CMD: microangiopathy and fibrosis are characteristic [16]. -Diffuse vascular involvement of the entire micro- and macrocirculation may be present [1•].	-Uncommon. -Sterile vegetations and nodular thickening of the mitral and aortic valves with regurgitation and MVP have been reported [16].	-Present in 8–12 %, due to pulmonary fibrosis or pulmonary vascular disease; the latter is associated with a worse prognosis [17].
Ankylosing spondylitis	-Due to ischaemic heart disease. Otherwise, the myocardium is rarely affected.	-Present in 9–45 % of the patients [19].	-Increased risk of CAD with a reported hazard ratio of 1.41 [20].	-Aortic root and valve disease in 82 % of patients [21] three forms: (1) AR due to proximal aortitis, (2) AR caused by aortic valvulitis and (3) MR due to thickening of the aortomitral junction (subaortic bump) [22].	-Increased risk not documented.

AR aortic regurgitation, *CMD* coronary microvascular dysfunction, *LVEF* left ventricular ejection fraction, *LVSD* left ventricular systolic dysfunction, *MR* mitral regurgitation, *TEE* transoesophageal echocardiography, *TTE* transthoracic echocardiography

Rheumatoid Arthritis

Ventricular Remodelling

RA is the most common inflammatory arthritis, and CV involvement can be present in 60 % of the patients [26]. Increased absolute and indexed left ventricular (LV) mass in patients with RA has been reported to be associated with increased risks of CV morbidity and mortality [27]. Compared to normal subjects, patients with RA are less likely to have normal geometry even after adjusting for cardiovascular risk factors and comorbidities, with concentric (LV) remodelling being the most prevalent abnormality [28]. The effect of RA on LV mass remains unclear because of inconsistent findings from the studies [27, 28]. Midtbo et al. showed that increased disease activity is associated with greater LV relative wall thickness independent of confounders such as hypertension, age and female gender [29]. As concentric LV remodelling is a strong and independent predictor of stroke, CV mortality and death, these findings underscore the importance of controlling disease activity in RA to prevent clinical CV events.

Greater diastolic LV diameter and aortic root diameter are observed in RA patients [6]. The aortic root diameter correlates positively with hypertension, disease duration and the ratio of transmitral Doppler early filling velocity (*E*) to tissue Doppler early diastolic annular velocity (*E*′) and negatively with transmitral early diastolic to atrial velocity (*A*) ratio which are indicative of elevated LV diastolic pressures [30].

Systolic Function and Myocardial Ischaemia

There is evidence for accelerated atherosclerosis in chronic inflammatory diseases, and this is well demonstrated in patients with RA [2]. Both traditional and non-traditional risk factors have been implicated [2]. RA is associated with a two to three times higher risk of myocardial infarction [5••] and a significantly higher prevalence of ST depression on resting electrocardiogram or Holter monitoring compared to controls [6]. In RA patients, ischaemia can be a result of atherosclerotic epicardial coronary artery disease (CAD) and/or CMD. The latter may be due to increased vasoconstriction, impaired vasodilation or vessel wall abnormalities [5••]. Thus, regional wall motion abnormalities and impaired coronary flow reserve (CFR) can occur in the absence of coronary stenosis [31, 32•].

On exercise echocardiography, patients with RA are more likely to have positive results for ischaemia compared with controls, a finding associated with increased mortality. Both rest and exercise wall motion score indices are increased in patients with RA, particularly in those with long disease duration [33]. In a study of asymptomatic patients with RA, dobutamine stress contrast echocardiography with wall-motion and perfusion evaluation was positive for ischaemia in 67 % of RA patients, significantly higher than controls (31 %) and comparable to patients with diabetes mellitus (78 %). RA patients with findings of ischaemia had higher C-reactive protein levels compared to those with negative stress tests [31].

Dipyridamole or adenosine stress Doppler echocardiography has been used to assess CFR which is defined as the ratio of coronary diastolic velocity at peak intravenous drug infusion to the coronary diastolic velocity at rest [23, 34]. A CFR < 2.0 is abnormal and indicates significant coronary artery stenosis or CMD when significant epicardial stenosis is not detected [23, 32•, 34]. It has good sensitivity and specificity for detecting CAD. The sensitivity increases further when combined with regional wall motion abnormalities [35]. Even patients with early RA (disease duration ≤12 months) and no clinical evidence of CAD or traditional risk factors have significant reduction in CFR—with a reported incidence of 24 % having a CFR of <2, consistent with significant coronary flow impairment [36]. In a recent study, Kakuta et al. identified CMD in 63 % of RA patients, 67 % of SLE patients and 76 % of SS patients [32•].

A diagnostic algorithm applicable to patients with rheumatologic disease and suspected myocardial ischaemia has been proposed to identify both those with CMD and/or CAD. A reduction in CFR with no inducible RWMA confirms CMD, while both reduced CFR and new RWMA suggests epicardial CAD and coronary angiography should be considered. Normal CFR in conjunction with no RWMA indicates absence of epicardial and microvascular disease [32•].

Asymptomatic patients with RA have lower LV ejection fraction (EF), mean velocity of circumferential fibre shortening and fractional shortening compared to controls [6]. Asymptomatic reduction in left ventricular ejection fraction (LVEF) is three times more common in RA patients than in the general population (13.5 % in RA patients versus 5.5 % in controls). LVEF was related to the presence of CAD in both RA patients and controls. Patients with decreased LVEF are less likely to be on methotrexate and corticosteroids [37]. Brain natriuretic peptide (BNP) levels and electrocardiographic abnormalities do not reliably identify RA patients with LV systolic dysfunction [38].

In RA patients with normal 2D transthoracic echocardiography (TTE) and no history of CV disease, ventricular radial and longitudinal systolic strains are reduced in comparison with matched controls [39, 40]. Strain abnormalities involving both the LV and right ventricle (RV) are reported to be associated with markers of RA disease severity, disease duration and need for disease modifying therapy [40, 41]. Increased apoptotic markers were associated with reduced longitudinal strain rate, and treatment with interleukin-1 inhibition led to a reduction in apoptotic markers and an improvement in longitudinal strain rate [42]. Longitudinal diastolic deformation parameters and radial diastolic deformation parameters were also

significantly reduced in patients with long-standing disease [41].

RA doubles the risk of developing heart failure after accounting for the presence of ischemic heart disease and CV risk factors [43]. In RA patients, causes for heart failure include focal non-specific, diffuse necrotizing or granulomatous myocarditis, drug-related cardiomyopathy and amyloidosis [3]. Considering the potential prognostic implications, echocardiographic screening of RA patients appears worthwhile.

Diastolic Function

LV diastolic dysfunction is reported in 76 % of RA patients [44]. In the majority of cases, it appears to be of grade I (abnormal relaxation pattern) [4]. In a recent meta-analysis involving patients with RA, prolonged isovolumetric relaxation time or a lower *E*/*A* ratio were the most frequently reported echocardiographic abnormalities, usually in the setting of preserved EF and some evidence of right heart involvement with either RV diastolic dysfunction or increased pulmonary pressure [4]. Diastolic dysfunction in RA patients is attributed to LV hypertrophy, interstitial fibrosis and ischaemia, but not to disease activity [37, 44]. Amyloid deposition, which is reported in 28 % of patients with RA, is another potential aetiology [4]. In patients with RA and no CV risk factors, diastolic dysfunction predicts adverse CV events and, therefore, a closer follow-up is recommended [44]. Diastolic dysfunction is also recognized as a key contributor to heart failure in these patients [45].

Valve Disease

Valvular involvement in RA may be more prevalent than previously thought [45]. Wisklowska et al. found valvular abnormalities in 47 % using TTE, while Roldan et al. reported a prevalence of 59 % using transoesophageal echocardiography (TEE) [6, 7]. The valvular abnormalities include leaflet thickening (diffuse or focal), valvular nodules and valvular regurgitation (Fig. 1). A recent meta-analysis showed a 10-fold increase in valvular nodules in patients with RA compared with controls [45]. The nodules are single or multiple, oval lesions, 4 to 12 mm in size with regular borders, homogenous echocardiographic reflectance and no calcification. They are usually located on the mitral and aortic valves [7]. Rheumatoid nodules can also be found in the epicardial fat, epicardium, myocardium, interventricular septum, chordae tendinae and aorta [3].

Valvular insufficiency is the main functional valvular abnormality in RA and predominantly affects left-sided valves (Fig. 1). Mitral or aortic regurgitation is common, with mild to moderate regurgitation in the majority of patients, although severe aortic regurgitation is a recognized complication in RA patients [7, 38, 46]. Mitral valve prolapse has been reported but is apparently a non-specific finding due to the prevalence of the abnormality in the general population [6, 7].

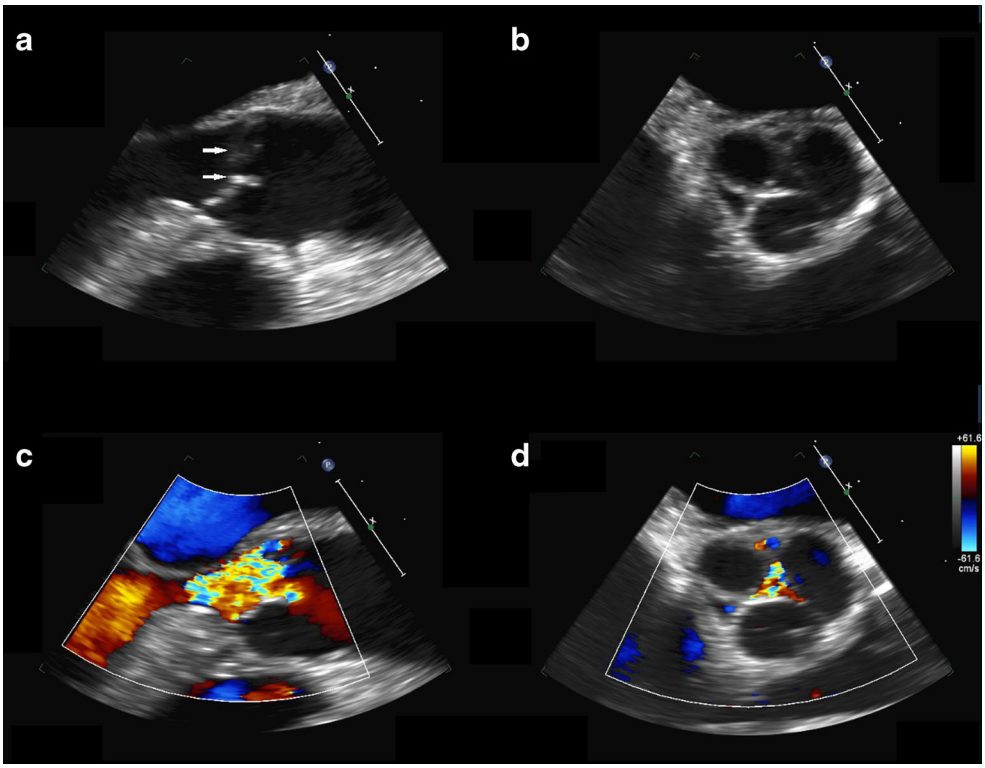

Fig. 1 This is a 69-year-old woman with rheumatoid arthritis and severe aortic regurgitation. Transoesophageal echocardiography in long-axis (**a**) and short-axis (**b**) views shows nodular thickening and retraction of the aortic cusps (*arrows*) with a central regurgitant orifice. Severe aortic regurgitation is confirmed by colour flow imaging (**c**, **d**)

Systemic Lupus Erythematosus

Systolic Function

Asymptomatic decreases in LVEF (≤50-55 %) on standard 2D-TTE are reported in 2.8 % of patients with SLE, with the lowest LVEF value being 42.5 % [47]. In a study involving patients with childhood SLE and normal EF on 2D-TTE [48], reduction in all parameters of LV longitudinal and radial deformation was demonstrated compared to controls. LV peak longitudinal systolic strain correlated negatively with SLE disease activity index and cumulative exposure to traditional and disease-related CV risk factors [48]. Abnormalities in RV strain have also been reported [11].

SLE patients have a 5–6-fold increased risk of CV events compared to the general population. The risk of myocardial infarction among women aged 35–44 years is increased by 50-fold [5••]. Premature epicardial CAD results from inflammation, traditional CAD risk factors and drug-related side effects [10]. Myocardial ischaemia may also result from arteritis, vasospasm, coronary thrombosis, embolization and CMD [10]. The role of echocardiography in the diagnosis of ischaemia follows the same principles as outlined in patients with RA.

Clinically apparent lupus myocarditis is rare, but subclinical myocarditis appears more common. Global hypokinesis on TTE or TEE in patients without evidence of CAD suggests this possibility. Cardiac magnetic resonance imaging shows delayed gadolinium enhancement in lupus myocarditis, but this feature is also observed in other forms of myocarditis. Biopsy has a low yield and treatment includes high-dose methyl-prednisolone and disease-modifying anti-rheumatic drugs. Cardiomyopathy in SLE patients can also be due to hypertension or ischaemia. Hydroxychloroquine-induced myocarditis can also occur but is rare at therapeutic doses [10].

Diastolic Function

LV diastolic dysfunction without clinically evident cardiac disease is increasingly reported in patients with rheumatologic diseases and represents one of the earliest and most common findings of subclinical cardiac involvement in these patients [9, 44, 49]. Diastolic dysfunction has been reported in up to 72 % of patients with SLE and has been linked to disease duration, but not to disease activity [12, 48, 49]. Patients with SLE and long disease duration have higher rates of impaired ventricular relaxation based on reduced transmitral E/A ratio, prolonged isovolumetric relaxation time and lower E'/A' ratio compared to those with short disease duration [50].

Valve Disease

In patients with SLE, valvular disease is common and echocardiographic abnormalities have been reported in up to 73 % of patients [24, 47, 50]. Findings include leaflet thickening (51–52 %), valvular masses (34–43 %), regurgitation (25–28 %) and stenosis (3–4 %) [50]. Although the majority of regurgitation is not severe [51•], on long-term follow-up, it may progress to severe in 12 % of the patients—a finding predictive of a poor outcome and associated with the presence of high levels of IgG anti-cardiolipin antibodies [24].

TTE detects vegetations in 30–40 % of the patients compared to 60–80 % by TEE [52]. The lack of pathological confirmation limits assessment of the sensitivity and specificity of TTE versus TEE [53]. Libman–Sacks vegetations appear as valve masses of varying shape, echodensity and size (from pinhead to 3–4 mm) that are attached to the valve leaflet surface and exhibit no independent motion (Fig. 2) [52, 53]. They are frequently located at the tip or mid-portion of the leaflets but may also involve the annulus, subvalvular apparatus and other endocardial surfaces of the heart [52, 53]. They have a propensity for the mitral and aortic valves and only rarely affect the right-sided valves [52]. Regurgitation is the common valvular dysfunction and stenosis is rare [51•, 52].

The differential diagnosis of Libman–Sacks lesions includes infective vegetations, changes of rheumatic heart disease, age-related degeneration and Lambl's excrescences. Infective vegetations are distinguished by their independent motion, homogenous echodensity and location at the line of leaflet closure, but occasionally, these may coexist with Libman–Sacks endocarditis in patients with SLE. In rheumatic heart disease, leaflet thickening is localized to the leaflet tips and there is chordal thickening, fusion, tethered motion and calcification. Calcification is common in age-related degenerative valvular disease, and the process commonly involves the annulus and becomes less extensive from the base to tip [54]. Lambl's excrescences are usually thinner (≤2 mm and rarely up to 3 mm), strand-like, homogeneous and highly mobile. They are located at the coaptation point at the atrial side of the mitral valve and ventricular side of the aortic valve. A cut-off >3 mm has been suggested to distinguish Libman–Sacks vegetations from Lambl's excrescences [51•].

3D-TEE is reported to be superior to 2D-TEE for the detection of Libman–Sacks vegetations, in terms of number and size of the vegetations and other associated abnormalities such as commissural fusion [51•]. Further studies are needed to validate the incremental value of 3D-TEE in SLE patients.

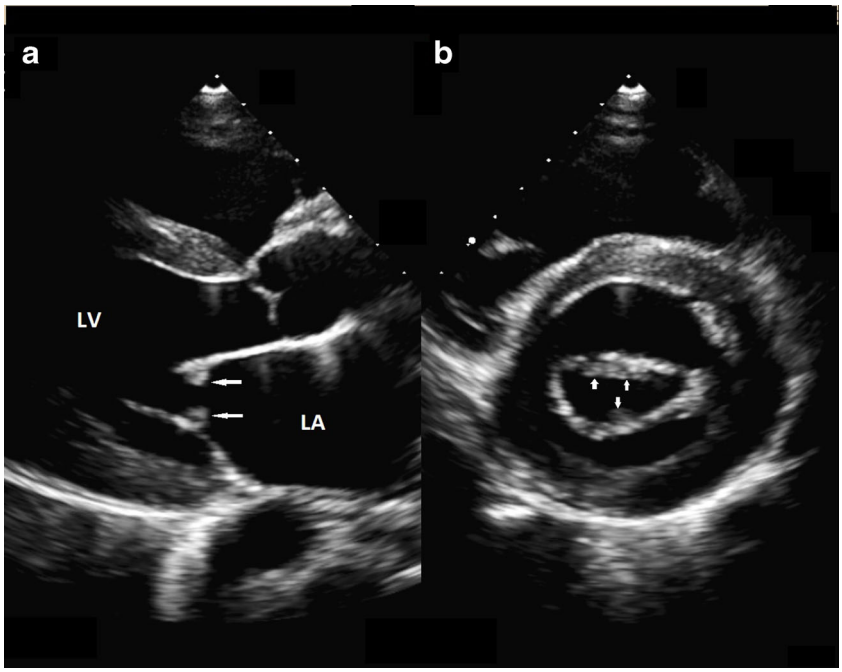

Fig. 2 This is a 20-year-old woman with systemic lupus erythematosus showing multiple small nodules (*arrows*) at the closure line of the mitral valve in the long-axis (**a**) and short-axis (**b**) views. These masses are typical of Libman–Sacks vegetations. *LA* left atrium, *LV* left ventricle

Pericardial Disease

Pericarditis is common in all rheumatological diseases. Pericardial effusion is observed in 4.6–50 % of patients with SLE, but cardiac tamponade is rare, occurring in <1 % (Fig. 3) [9, 55, 56]. Symptomatic pericardial effusion occurs more commonly within the first year of diagnosis and predicts reduced survival (5-year survival of 46 %). TTE-guided pericardiocentesis is safe and effective in large symptomatic pericardial effusions, and treatment of underlying SLE with non-steroidal anti-inflammatory agents, corticosteroids and steroid-sparing agents is often effective in smaller effusions [56]. Pericardial thickening is reported in 38 % of the patients [10].

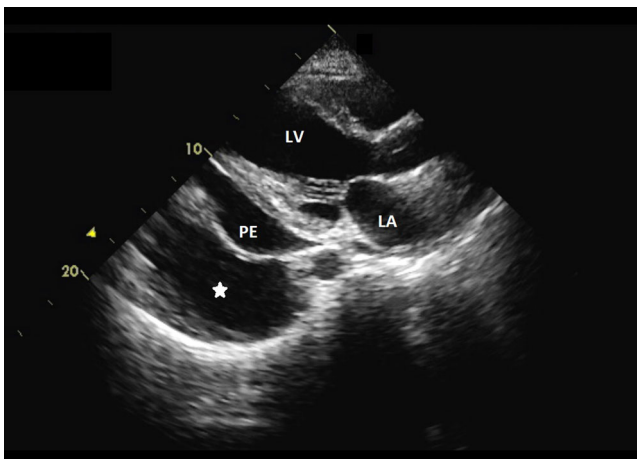

Fig. 3 This is a 43-year-old woman with systemic lupus erythematosus, showing the presence of pericardial effusion and pleural effusion (*). *LA* left atrium, *LV* left ventricle, *PE* pericardial effusion

APAS

Cardiovascular disease is reported in 50–75 % of patients with APAS and manifests mainly as peripheral venous, arterial and/or intracardiac thrombosis.

Ventricular Function and Myocardial Ischaemia

Ventricular dysfunction in patients with APAS may result from ischaemia, increased aortic stiffness, pulmonary hypertension or reduced LV preload [14]. Ischaemia may be caused by coronary thrombosis, embolism, accelerated atherosclerosis or CMD. Coronary embolism is the most frequent

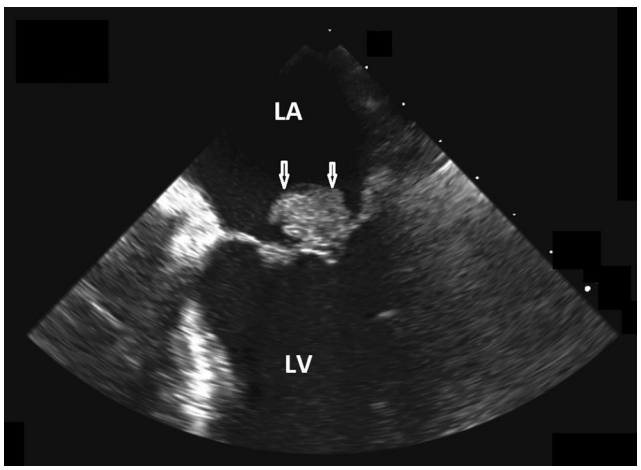

Fig. 4 This is a 50-year-old woman with anti-phospholipid antibody syndrome presenting with a stroke. Transoesophageal echocardiogram shows a large mobile mass on the mitral valve (*arrows*). *LA* left atrium, *LV* left ventricle

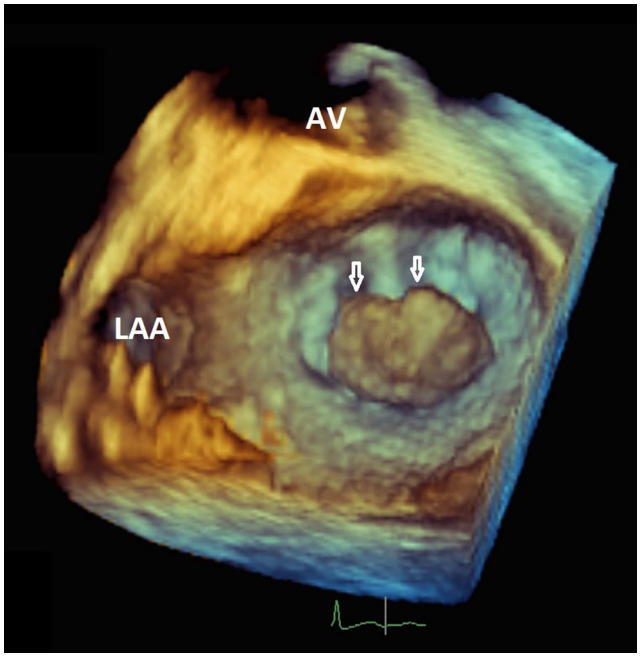

Fig. 5 Transoesophageal 3D view from the left atrial perspective shows a large mass attached to the atrial surface of the mitral valve (*arrows*). This is the same patient as in Fig. 4

aetiology of myocardial ischaemia in young patients with APAS [13•, 14]. The presence of high titres of antiphospholipid antibodies, particularly aβ2GPI antibodies, has been linked to accelerated atherosclerosis and to myocardial necrosis due to microvascular damage or myocardial infarction from CAD [13•].

Valve Disease

APAS-related valvulopathy can present as valvular regurgitation or stenosis occurring in association with valvular abnormalities, which include leaflet thickening (>3 mm involving the proximal or middle leaflet) and/or irregular nodules on the atrial surface of the mitral valve and/or the ventricular surface of the aortic valve [13•, 53]. In one study, 84 % per cent of the primary APAS patients had functional or structural valvular defects, predominantly involving the mitral valve [15].

Histologically, the lesions of APAS are predominantly thrombotic but can be inflammatory or mixed in nature. They may be asymptomatic or cause overt disease and can be distinguished from Libman–Sacks vegetations which are due to valvulitis with prominent inflammatory cell infiltration unlike the largely bland lesions of APAS [13•].

Vegetations are reported in up to 40 % of APAS patients and are usually solitary and large but may be multiple (Figs. 4 and 5). They may be sessile or mobile and may change in appearance, resolve or reappear over time. Left-sided valves are more commonly affected, likely due to higher shear stress [13•]. The vegetations form on structurally normal or abnormal valves [57]. Clinically significant valvular dysfunction is reported in 3–5 % of patients [13•].

Contrary to rheumatic valvular changes, APAS lesions involve the base to mid-portion of the leaflet and are not associated with leaflet fusion or calcification. They do not involve the chordal apparatus. The lesions may be distinguished from infective vegetations by their broad base and lack of tissue destruction, chordal rupture or abscess formation. In APAS, valve abnormalities are a risk factor for stroke [15].

Intracardiac Thrombosis

Intracardiac abnormalities in APAS patients include atrial spontaneous echocardiographic contrast in patients in sinus rhythm and atrial or ventricular thrombi that may be adherent, free floating or obstructive [57]. Intracardiac thrombosis, similar to valvular masses, is a potential source for systemic embolization. Echocardiographic follow-up is therefore indicated in APAS patients [14].

Systemic Sclerosis

Systolic Function

Asymptomatic LV systolic dysfunction is reported in 7 % of the patients with SS [16]. Myocardial fibrosis in a mosaic patchy distribution is considered pathognomonic of SS. The fibrotic areas do not correlate with a single coronary artery territory. Foci of contraction band necrosis also occur [16]. It is suggested that reversible vasospastic abnormalities, as well as fixed vascular abnormalities due to fibrosis or abnormalities of small coronary vessels, contribute to the myocardial disease [17]. Premature CAD and CMD also occur in SS.

Diastolic Function

Diastolic dysfunction is detected in 17.4–55 % of the patients with SS [16, 18] and is a marker of increased risk of death, with a reported hazard ratio of 3.2 per each standard deviation decrease in tissue Doppler E' velocity. Factors independently associated with diastolic dysfunction in SS include disease duration, age, CAD and systemic hypertension [58].

Valve Disease

Valvular abnormalities are uncommon in patients with SS. Sterile vegetations, nodular thickening of the mitral and aortic valves, and mitral valve prolapse have been reported in SS and may occur in association with severe myocardial damage. While the clinical significance of these findings in patients with SS is not well delineated, association with systemic embolism has been reported [16].

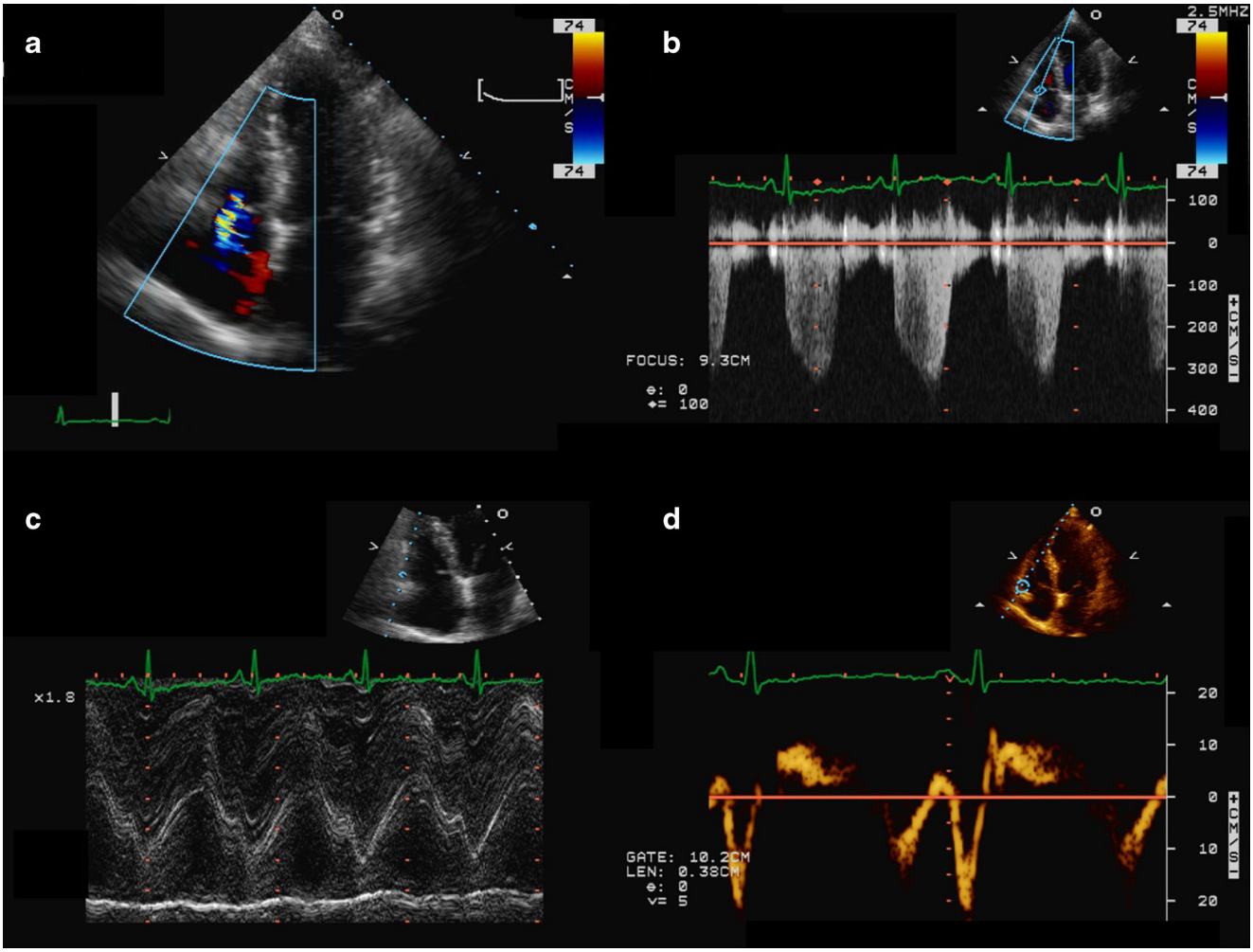

Fig. 6 This is a 54-year-old woman with systemic sclerosis. **a** The right ventricle was normal in size, but mild tricuspid regurgitation was present. **b** The right ventricular systolic pressure was 50 mmHg based on the tricuspid regurgitation velocity. Tricuspid annular plane systolic excursion (**c**) was 22 mm and right ventricular annular velocity (**d**) 10 cm/s, confirming normal right ventricular function

Pulmonary Hypertension

Pulmonary hypertension occurs in 8–12 % of patients with SS [8]. It is recommended that asymptomatic patients with SS should be screened for pulmonary hypertension on an annual basis [59•]. In the presence of symptoms and/or signs of pulmonary hypertension, a tricuspid regurgitation (TR) jet velocity of 2.5–2.8 m/s (trans-tricuspid gradient of 25 to 32 mmHg) indicates referral for a right heart catheterization (RHC), while in asymptomatic patients, a TR jet velocity >2.8 m/s (transtricuspid gradient of >32 mmHg) is taken as the cut-off value. Patients with right atrial enlargement (major dimension > 53 mm) or RV enlargement (mid cavity dimension > 35 mm) should be referred for right heart catherization (RHC) irrespective of TR jet velocity or when the TR jet is absent [59•]. False negative and false positive results have been reported on 2D-TTE and, thus, echocardiographically derived RV systolic pressure measurements should not be solely relied on for diagnosing pulmonary hypertension [60••].

Screening accuracy can be improved by the addition of other parameters to TTE—including pulmonary function testing, BNP levels and other clinical variables [61]. In the DETECT study involving patients with SS at high risk for pulmonary hypertension, a two-step detection algorithm was developed using clinical variables and two echocardiographic variables to determine indications for RHC. The DETECT algorithm had a high sensitivity for detection of pulmonary hypertension, including mild cases, and missed only 4 % of the cases [62•].

Besides assessment of RV systolic pressure, 2D-TTE can detect other signs suggesting pulmonary hypertension—such as the RV enlargement (RV/ LV basal diameter ratio >1.0), flattening of the interventricular septum (LV eccentricity index >1.1 in systole and/or diastole), pulmonary artery acceleration time <105 m/s, pulmonary midsystolic notching, early

diastolic pulmonary regurgitation velocity >2.2 m/s, pulmonary artery diameter >25 mm, dilated inferior cava (diameter >21 mm with decreased inspiratory collapse) and dilated right atrium (end systolic area >18 cm^2). A comprehensive 2D-TTE assessment should also include determination of other variables—including the Tei index, tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change and longitudinal systolic strain and strain rate (Fig. 6) [60••].

Speckle tracking echocardiography improves assessment of RV function and, in patients with pulmonary hypertension, may have clinical implications. Recently, Fukuda et al. in a study involving 82 patients with pulmonary hypertension who underwent echocardiography and RHC found that right atrial strain in patients with pulmonary hypertension correlated with mean right atrial and RV end-diastolic pressures. Furthermore, global right atrial and RV strains were correlated with clinical outcome [63]. In a 5-year prospective study, Kusunose et al. reported that 6-min walk stress echocardiography provided an incremental prognostic value for predicting future pulmonary hypertension development in patients with rheumatologic diseases. Six-minute walk distance, early diastolic tricuspid annulus velocity and the change in mean pulmonary artery pressure in relation to cardiac output were associated with the future development of pulmonary hypertension [64•].

Ankylosing Spondylitis

Systolic and Diastolic Function

In patients with ankylosing spondylitis (AS), LV diastolic and systolic strain values are reported to be reduced, despite normal EF and no clinical evidence of CV disease. Diastolic dysfunction is reported in 9–45 % of patients with AS [19]. In the majority of cases, it appears to be grade I (abnormal relaxation pattern) and is associated with smoking, high body mass index and hypertension [65, 66]. A recent meta-analysis showed a 41 % excess risk of CAD in AS patients [20]. CFR is also reduced and correlates well with C-reactive protein and TNF-alpha levels, suggesting that CFR is an early indicator of CV involvement in AS patients [21].

Aortic Root and Valve Disease

Aortic root and valve disease are common in patients with AS, occurring in 82 % of the patients, including aortic root thickening, increased aortic stiffness and dilatation. Valve thickening may be detected in 41 % of the aortic valve and 34 % of the mitral valve, predominantly as nodularities of the aortic cusps and basal thickening of the anterior mitral leaflet forming the characteristic subaortic bump [22, 67]. Valve disease in patients with AS can be classified into three categories: (1) aortic regurgitation secondary to proximal aortitis leading to aortic root thickening, stiffness, dilatation and, rarely, aneurysm formation; (2) aortic regurgitation resulting from aortic valvulitis causing cusp thickening and retraction; and (3) mitral regurgitation due to thickening of the aortomitral junction (subaortic bump) causing retraction and decreased mobility of the anterior mitral leaflet and incomplete leaflet coaptation [22, 67]. Early in the course of the disease, only thickening of the aortic and mitral valve leaflets is observed without regurgitation or clinical cardiac manifestations [67]. Upon long-term follow-up, aortic root or valve abnormalities may develop or progress, although resolution has been reported in some patients [22].

Conclusions

Patients with rheumatologic diseases are a heterogeneous group of patients at an increased risk of adverse CV events leading to mortality and morbidity. In caring for these patients, it is crucial to be aware of the full spectrum of CV manifestations of the conditions, including structural, functional and subclinical abnormalities. The data on CV involvement in these patients are impressive, though at times conflicting. Disparate findings are likely accounted for by differences in patient characteristics, disease severity, disease duration, background therapy, diagnostic criteria and imaging modalities. Further studies investigating the clinical implications of echocardiographic findings and the value of echocardiographic screening are warranted.

Compliance with Ethical Standards

Conflict of Interest Maha A. Al-Mohaissen and Kwan-Leung Chan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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