


Imaging for screening cardiovascular involvement in patients with systemic rheumatologic diseases: more questions than answers

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Cardiovascular involvement due to systemic rheumatologic diseases (SRDs) remains largely underdiagnosed despite causing excess mortality and limiting the favourable effect of therapeutic developments on survival. Traditional risk scoring systems are poorly calibrated for SRD patients. There is an unmet need to develop a cardiovascular (CV) risk stratification tool and screening algorithm for CV involvement dedicated to asymptomatic patients with SRDs. Even though accelerated atherosclerosis is the most prominent cause of major CV events, a more comprehensive approach is crucial to detect different pathological processes associated with SRDs that are leading to CV complications. In that regard, incorporation of imaging parameters obtained from echocardiography and carotid ultrasound (CUS) might help to improve risk models, to detect and monitor subclinical CV involvement. These two imaging modalities should be an integral part of screening SRD patients with suspicion of CV involvement on top of electrocardiogram (ECG). Cardiac magnetic resonance and multi-slice computerized tomography angiography and nuclear imaging modalities seem very important to complement echocardiography and CUS for further evaluation. However, to answer the question ‘Should asymptomatic patients with SRDs undergo screening with echocardiography and CUS on top of ECG?’ necessitates large studies performing cardiac screening with a standard approach by using these imaging methods to obtain longitudinal data with hard CV outcomes.

Keywords rheumatologic diseases • risk assessment • cardiovascular complications • multimodality imaging

Introduction

Cardiovascular (CV) system can be involved by many aspects during the course of systemic rheumatologic diseases (SRDs) (Table 1). CV complications are associated with excess mortality and limit the favourable effect of therapeutic developments on survival in SRDs. Yet, CV involvement remains underestimated or silent most of the time.¹ Monitorization of subclinical CV diseases and early diagnosis might protect from the dismal course related to CV complications by modifying the therapeutic approach.² This review focuses on the rational and potential yields of imaging as part of screening CV involvement in SRDs and highlights gaps in evidence.

Rationale for screening atherosclerotic CV disease

Accelerated atherosclerosis has long been known as the leading cause of excess mortality in SRDs, particularly in those with inflammatory arthritis.³ Inflammation acts synergistically with traditional risk factors to promote atherosclerosis and the control of inflammatory activity has been shown to reduce the residual risk of recurrent CV events on top of optimal control of traditional risk factors.^{2,4} There is higher rate of incident CV events,⁵ case fatality,^{6,7} and recurrences after an index event, even when patients are managed similarly

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Table 1 Targets for screening cardiovascular involvement in systemic rheumatologic diseases

	Major	Other
Rheumatoid arthritis	Accelerated atherosclerosis Heart failure	Amyloidosis Myocarditis Pericarditis Valvular lesions
Spondyloarthropathies	Accelerated atherosclerosis Valvular lesions (aortic regurgitation)	Rhythm abnormalities Heart failure
Systemic lupus erythematosus	Accelerated atherosclerosis Valvulitis/Valvular lesions Pulmonary arterial hypertension Microvascular dysfunction Pericarditis	Myocarditis Coronary vasculitis/thrombosis Rhythm abnormalities
Systemic sclerosis	Pulmonary arterial hypertension Microvascular dysfunction Cardiomyopathy/heart failure	Rhythm abnormalities Pericarditis Valvular lesions? Accelerated atherosclerosis?
Antiphospholipid syndrome	Valvular lesions	Coronary thrombosis
Systemic vasculitis		
Large vessel vasculitis	Aortic aneurysms Valvular lesions (aortic regurgitation) Cardiomyopathy	Coronary arteritis Group IV pulmonary hypertension
Medium size vessel vasculitis	Cardiomyopathy Coronary vasculitis Coronary aneurysms (Kawasaki disease)	Pericarditis
Small vessel vasculitis	Heart failure Microvascular dysfunction	Pericarditis Endocarditis (Churg–Strauss syndrome)

and despite having similar classical risk factors in rheumatoid arthritis (RA) patients as compared to their non-RA counterparts.⁸ Likewise, patients with systemic lupus erythematosus (SLE) are at increased risk for myocardial infarction and stroke.⁹ Importantly, female gender is preponderant and patients with SRDs are younger than the general population having comparable severity of atherosclerosis¹⁰ (Figure 1, [Supplementary data](#) online, *Video S1*). Of note, the excess risk of mortality from CV events in patients with RA and SLE was shown to be comparable to the risk associated with type 2 diabetes mellitus.^{6,11}

This malignant course is partly explained by vulnerable plaques prone to rupture with excess inflammatory activity as shown in pathologic specimens, despite less severe stenotic lesions.¹² Consequently, the presentation is atypical with more frequent silent myocardial infarction, sudden cardiac death despite less frequent angina,¹ explaining the poor outcome after CV events and limited success of secondary prevention.⁴ Vigilant and aggressive assessment of risk and subclinical CV involvement in patients with SRDs seems therefore indispensable. However classical risk scoring systems are poorly calibrated for SRD patients, reaching almost 50% underestimation by Framingham score in patients with RA and SLE.^{13,14} Patients who are mostly women with persistently elevated inflammatory markers are placed at low risk categories by age and gender giving a false sense of security. Although not validated, the proposed solution by EULAR (European League Against Rheumatism) to improve risk stratification is to introduce a multiplication factor of 1.5

when using the Framingham or European SCORE systems for patients with RA.¹⁵ This approach is extended to all SRDs as Class IIb indication in European Society of Cardiology (ESC) guidelines for CV prevention¹⁶ despite the lack of use of any multiplier for SRDs in American College of Cardiology/American Heart Association (ACC/AHA) prevention guidelines.¹⁷

Imaging for screening atherosclerotic CV disease

There is low level of agreement for the use of carotid ultrasound (CUS) for risk stratification and screening asymptomatic carotid plaques in patients with RA in EULAR recommendations and no imaging is recommended for screening CV disease for SRD in general.¹⁵ Yet, in two large studies, CUS findings re-classified RA patients into more appropriate CV risk groups.^{18,19} In addition, evidence shows that; (i) carotid intima media thickness is a robust marker of atherosclerosis in large populations,¹⁸ (ii) carotid plaques are prevalent in patients with SRDs, have rapid progression, particularly in association with high levels of systemic inflammation,²⁰ and (iii) carotid atherosclerosis predicts incident acute coronary syndromes in RA.²¹ On the other hand, higher coronary calcium scores have been found in patients with established RA and SLE than those with early or no disease.^{22,23} However, coronary calcium score is not sensitive for vulnerable

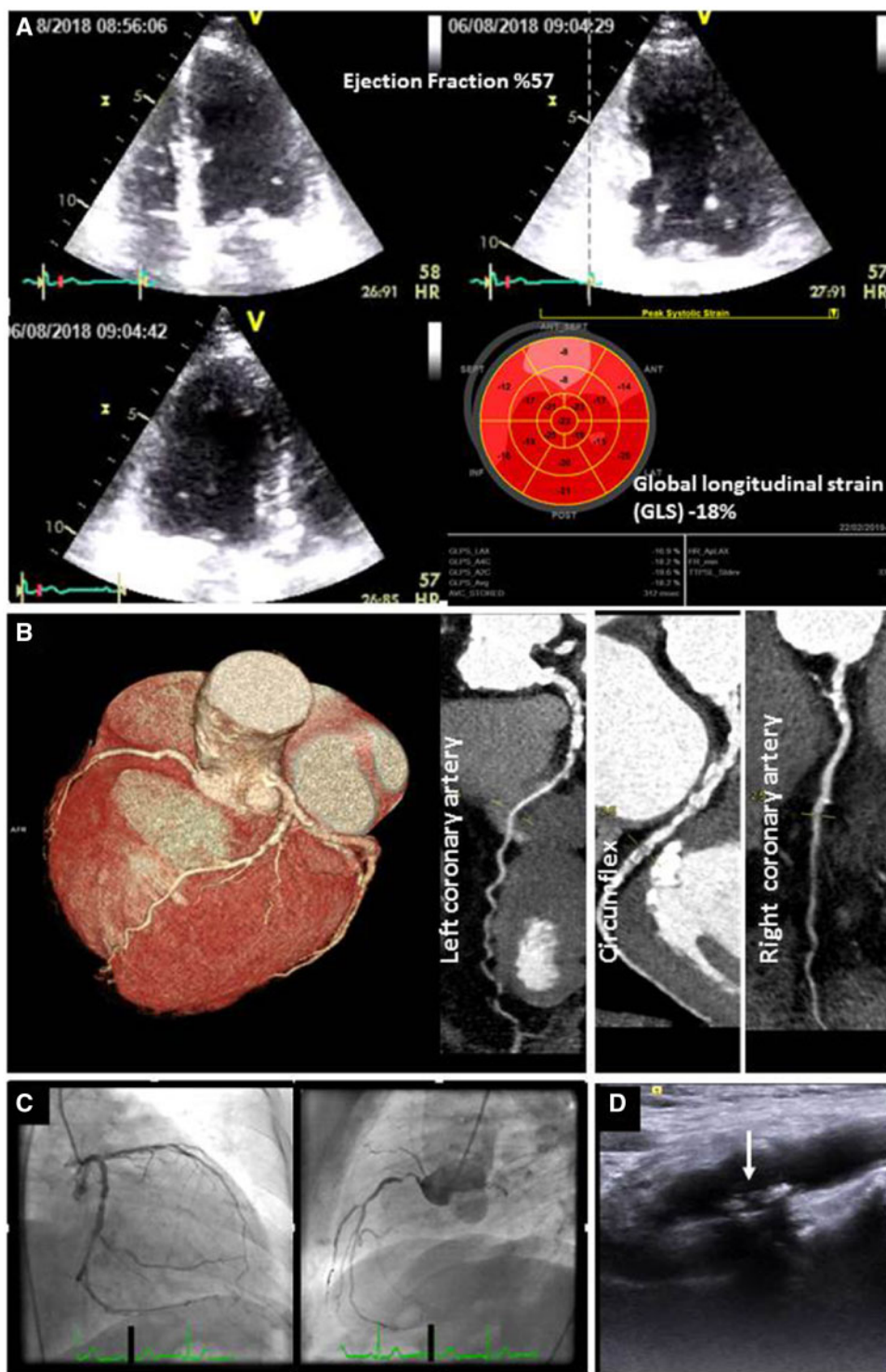


Figure 1 A 48-year-old woman, suffering from rheumatoid arthritis for 10 years, apparently asymptomatic with severe functional disability due to joint pain and no traditional risk factors for atherosclerosis (A). Mildly reduced global longitudinal strain with subtle segmental heterogeneity, no visual wall motion abnormality. (B) Multi-slice computerized tomography angiography and (C) conventional angiography confirms severe three-vessel disease. (D) Carotid plaques of the patient (arrow).

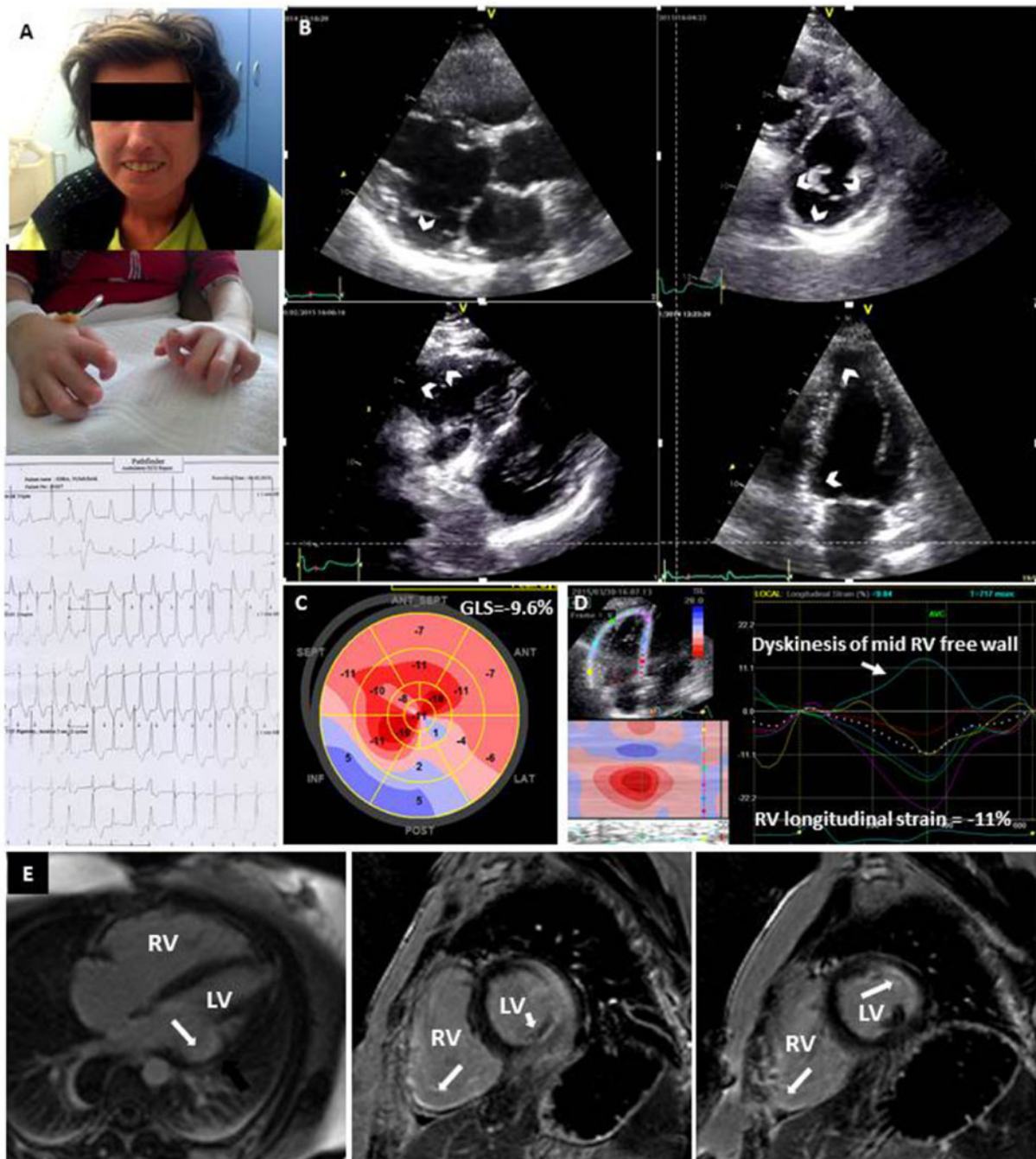


Figure 2 (A) A 36-year-old woman with palpitation, suffering from systemic sclerosis for 15 years, had multiple episodes of non-sustained ventricular tachycardia on Holter. (B) Severe regional wall motion abnormalities in left (LV) and right ventricle (RV) (arrows). (C, D) Global longitudinal strain (GLS) shows severe regional LV and RV systolic dysfunction. (E) Cardiac magnetic resonance shows enlarged RV and transmural late gadolinium hyperenhancement on both LV and RV walls (arrows) despite no significant epicardial coronary lesion or pulmonary hypertension.

is a method that increases the sensitivity of echocardiography for detecting subclinical myocardial dysfunction when ejection fraction is still preserved, irrespective of underlying mechanism. Preliminary data suggest that echocardiography with STI could be a promising tool for screening early myocardial involvement and for monitoring the effects of anti-inflammatory treatment in SRDs.^{36,37}

CMR, PET, and PET/CMR enable tissue characterization and help to differentiate inflammation, fibrosis, and oedema from ischaemic lesions (Figure 4, Supplementary data online, Video S4).^{34,38-40} However, there is not enough evidence to counterbalance the cost and limited availability of CMR or PET as screening and serial follow-up tools to assess myocardial involvement in asymptomatic SRD

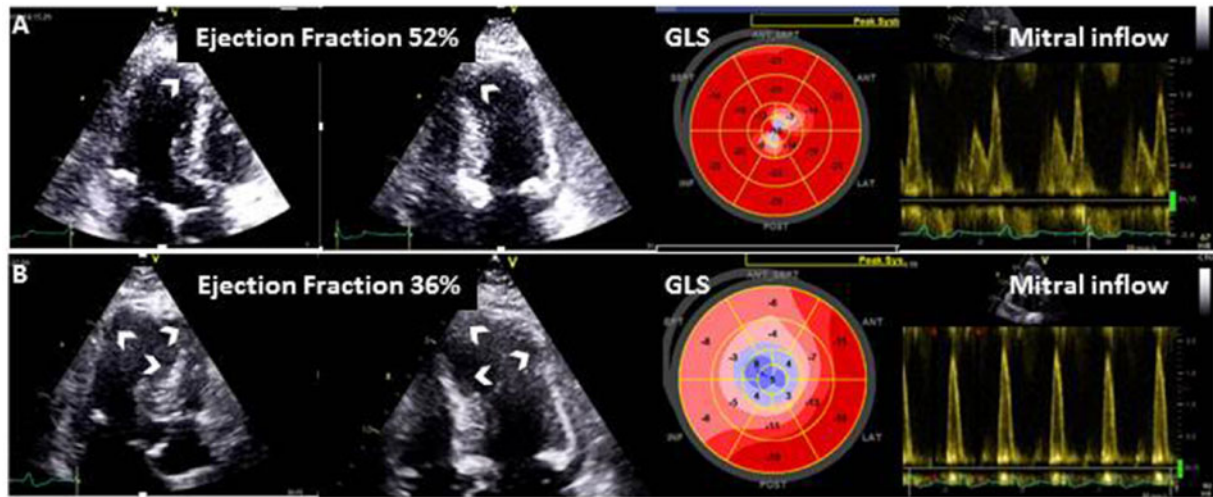


Figure 3 A 50-year-old woman with systemic sclerosis, clinically stable over the last 10 years. (A) Asymptomatic during next to last visit, mild wall motion abnormality at the apex. (B) Chest pain 4 months later, severe regional wall motion abnormalities and restrictive diastolic function despite normal coronary angiography. GLS, global longitudinal strain.

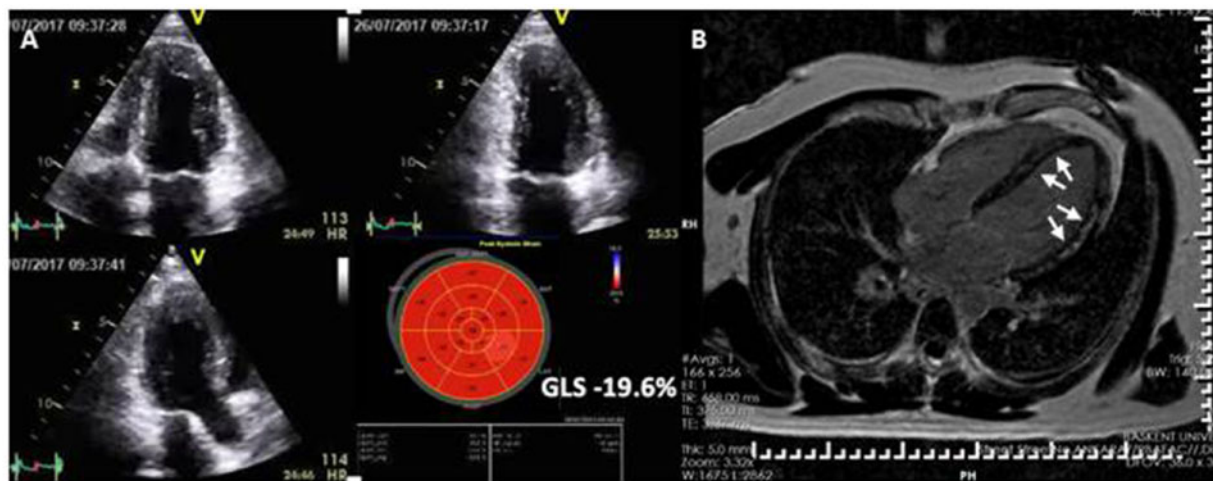


Figure 4 Lupus myocarditis in a 32-year-old woman with chest pain, arrhythmias, elevated C-reactive protein, troponins, and normal coronaries. (A) 2D echocardiography shows normal systolic function, but global longitudinal strain (GLS) is at the lower limit of normal. (B) Cardiac magnetic resonance shows extensive mid-wall late gadolinium hyperenhancement (arrows).

patients. Of note, these tools can be more accurate than echocardiography in SRD patients with predominant right ventricular (RV) inflammation, fibrosis, or dysfunction due to pulmonary hypertension (PH).³⁶

Rational for screening valvular involvement

Valvular involvement is common in SRD patients reaching a frequency of 80% in SLE by transoesophageal echocardiography.⁴¹

Valvular regurgitation is the most frequent consequence. Progression to surgery is around 4–10%.⁴² Antiphospholipid antibody positivity significantly increases the risk of valvulitis and endocarditis.⁴³ Libman–Sacks endocarditis (non-bacterial vegetations) that can be encountered in up to 11% of SLE patients,⁴⁴ is an independent cause of stroke and associated with mortality in SLE and antiphospholipid syndrome (APLS) (Figure 5, Supplementary data online, Video S5).^{41,45} Aortic regurgitation is an important complication of ankylosing spondylitis and large vessel vasculitis (LVV) mainly in association with root dilatation and/or extension of fibrosis into the valve.⁴⁶



Figure 5 Libman–Sacks vegetations on both sides of mitral leaflet tips (arrows) in a 48-year-old woman with antiphospholipid syndrome and acute ischaemic stroke.

Most of the valvular abnormalities are clinically silent and overlooked without echocardiography although acute aortic or mitral valvulitis can be the initial presentation particularly in SLE and AS.^{46,47} Infective endocarditis should always be considered in these immune compromised patients particularly in those with underlying valvulopathy in case of clinical deterioration.

Imaging for screening valvular involvement

Echocardiography is key to detect and characterize valvular damage and has been recommended as a screening tool for valvular pathologies in asymptomatic patients with APLS and SLE.^{43,44} Typical valvular lesions include fibrotic thickening, retraction of the leaflets, nodules, or sterile vegetations most frequently effecting mitral and aortic valves.^{27,47} Tricuspid valve can also be involved (Figure 6, Supplementary data online, Video S6A, B). However, no evidence supports routine assessment of valvular involvement in other asymptomatic SRD patients without relevant findings.

Rationale for screening PH

PH is a poor prognosticator irrespective of its cause. All groups of PH can be encountered as a complication of SRD. Pulmonary arterial hypertension (PAH) is an important cause of mortality particularly in SSc affecting 6–12% of the patients.⁴⁸ Other than PAH, LV dysfunction and pulmonary involvement can cause PH in SSc. The presence of antiphospholipid antibodies increases the risk for chronic thrombo-embolic PH. Moreover, vasculitis of large pulmonary arteries can cause PH in Takayasu's arteritis (TA).⁴⁹ Early diagnosis by screening PH in SSc has been shown to impact survival and patient management.⁵⁰

Imaging for screening PH

Yearly echocardiographic screening is only recommended for detecting PH related to SSc spectrum disorders by the European

guidelines.^{51,52} In other SRDs, echocardiographic screening for PH is indicated only if patients are symptomatic. Echocardiography also provides information about the LV dysfunction which is the most common cause of PH. RV adaptation to elevated pulmonary artery pressure is not uniform among patients and is the main determinant of survival in PAH including SRD patients. Other imaging modalities, particularly CMR, are complementary to echocardiography to define RV function and to help the differential diagnosis of PH.⁵³

Pericardial involvement

Pericardial effusion and pericarditis are frequent in SRDs, whereas haemodynamically significant effusions or chronic constrictive pericarditis are unlikely.⁴⁷ Imaging for pericardial involvement is useful for the differential diagnosis of chest pain. Documentation of pericardial involvement could help to make the diagnosis of SRDs, particularly SLE. Pericardial effusion is a poor prognostic factor in patients with PAH.⁵¹ However, no evidence supports screening asymptomatic SRD patients for pericardial involvement. Computerized tomography and CMR are complementary to echocardiography to assess the size and location of effusion, pericardial thickness, or calcification whenever needed in symptomatic patients.

Rational for screening large vessels

Giant cell arteritis (GCA) and TA are the most common LVVs, characterized by involvement of aorta and its main branches. Aortic aneurysms are common in GCA than TA, both can cause vascular stenosis and occlusions.⁵³ Stroke or acute coronary syndrome can be the initial manifestation. Pulmonary arterial lesions can lead to group IV PH in TA.⁴⁹ Cardiac complications including cardiomyopathy and severe hypertension are among major causes of mortality in TA.⁵⁴ Behçet's syndrome is another vasculitis that can cause pulmonary artery and aortic aneurysms and stenoses.⁵⁵ Isolated aortitis or LVV secondary to SRDs as a rare manifestation, can also be seen. As patients can be asymptomatic, early documentation of pathologies are critical for intensifying treatment such as vigorous control of hypertension or optimizing immune suppression.

Imaging for screening large vessels

Ultrasound of temporal and axillary arteries is useful for the diagnosis of cranial GCA. Magnetic resonance is recommended for documentation of vasculitic involvement in aorta and its branches. PET, MCTA, and/or ultrasound may be used as alternative modalities. All of the above imaging modalities have the capability to document inflammation and complications of LVV.⁵⁶ Addition of echocardiographic screening in the initial workup might help to detect cardiac complications of LVV (Figure 7, Supplementary data online, Video S7A, B) whereas no evidence supports the use of transoesophageal

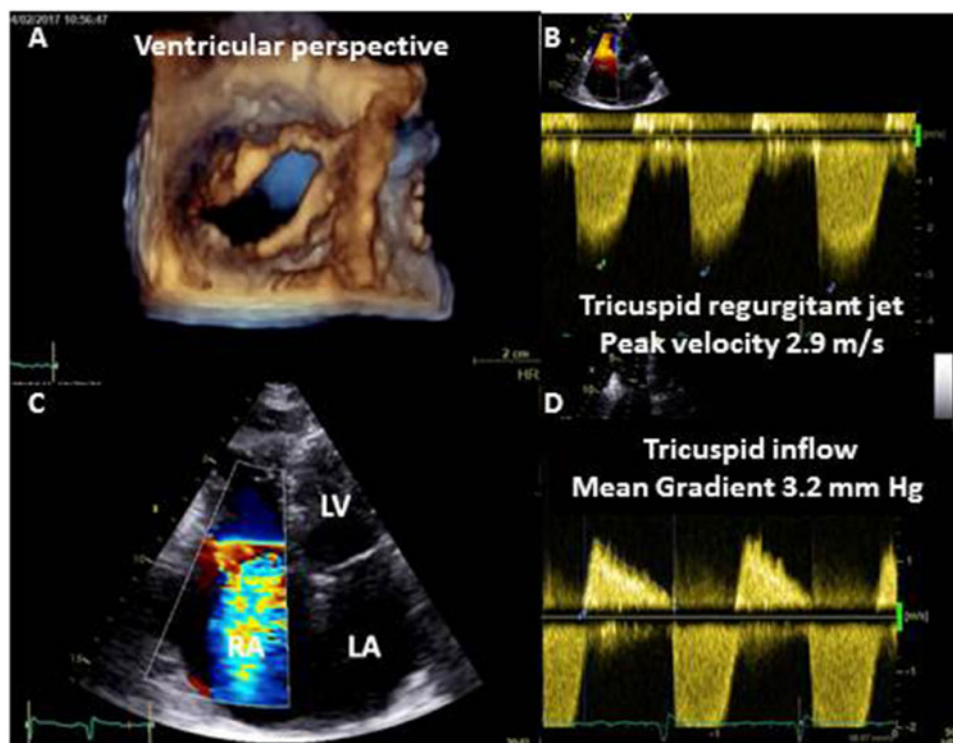


Figure 6 Lupus valvulitis. (A) Thickened, fibrotic, retracted tricuspid leaflets with (B, C) severe regurgitation and (D) mild stenosis. Mitral leaflets were less severely affected in this patient. LA, left atrium; LV, left ventricle.

echocardiography for screening structural abnormalities of the aorta in asymptomatic patients.

General comments

CV involvement due to SRDs remains largely underdiagnosed despite high rates of CV complications leading to poor survival. Traditional risk scoring systems underestimate CV risk in SRD patients. Primary prevention guidelines recommend clinical judgement to be applied on a case-by-case basis regarding the impact of imaging for screening patients with SRDs, except for PH in SSc.^{16,17,51} Rigorous CV risk assessment and early referral to a cardiologist are key to optimize the outcome. Although accelerated atherosclerosis is the most prominent cause of major CV events, the contribution of other causes of cardiac pathologies should also be considered (Figure 8).

Echocardiography and CUS or calcium score, in addition to ECG, should be an integral part of screening in SRD; especially in RA, SLE, and SSc patients with suspicion of CV involvement. Echocardiography has great potential to detect subclinical myocardial dysfunction, valvular, macro- and microvascular damage by means of its versatile use at a low cost, free of radiation, and nephrotoxicity. The addition of CUS to traditional risk scoring systems, improves risk estimation for atherosclerotic complications in these patients. CMR, MCTA and nuclear imaging complement echocardiography and CUS to obtain more data about CV complications. They should also be considered

whenever the level of suspicion remains high despite inconclusive echocardiographic and/or CUS findings (Figure 9).

Future research and gaps in evidence

Development of a CV risk stratification tool and screening algorithm dedicated to asymptomatic patients with SRDs is an unmet need. In that regard, imaging parameters obtained from echocardiography and CUS or calcium scoring might help to improve risk models, to detect, and monitor subclinical CV involvement. Certainly, some CV abnormalities are more progressive and life threatening than others and necessitate closer follow-up. But those have been incompletely defined so far. Existing imaging studies in SRDs have heterogeneous outcome measurements, inclusion criteria, follow-up durations, and different patient populations and do not allow to pool the data to define the prevalence, incidence, and progression of CV diseases related to SRDs and to conduct insightful meta-analyses. So far, the answer to 'Should asymptomatic patients with SRDs undergo screening with echocardiography and CUS on top of ECG?' remains an extrapolation of the pieces of evidence from heterogeneous studies. Obviously, large studies performing cardiac screening with a standard approach by using echocardiography and CUS to obtain longitudinal data with hard endpoints are awaited in order to implement imaging

In conclusion, more questions than answers remain to be explored to formulate CV prevention guidelines dedicated to SRD patients and to optimize the outcome where CV imaging seems to be pivotal.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: none declared.

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