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Concise report

Incidental significant arrhythmia in scleroderma associates with cardiac magnetic resonance measure of fibrosis and hs-TnI and NT-proBNP

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Abstract

Objectives. To screen for significant arrhythmias with an implantable loop recorder (ILR) in patients with SSc and no known cardiovascular disease, and identify associated disease phenotype, blood and cardiovascular magnetic resonance (CMR) biomarkers.

Methods. Twenty patients with SSc with no history of primary SSc heart disease, traditional cardiovascular disease, diabetes or maximum one traditional cardiovascular risk factor underwent clinical assessment, contrast-enhanced CMR and ILR insertion.

Results. ILR data were available for 19 patients: 63% female, mean (S.D.) age of 53 (12) years, 32% diffuse SSc. Eight patients had significant arrhythmias over 3 years: one complete heart block, two non-sustained ventricular tachycardia [all three dcSSc, two anti-topoisomerase antibodies (Scl70) positive, three interstitial lung disease and two previous digital ulceration] and five atrial arrhythmias of which four were with limited SSc. These required interventions with one permanent pacemaker implantation, four anti-arrhythmic pharmacotherapy, one anticoagulation.

Patients with significant arrhythmia had higher baseline high-sensitivity troponin I and N-terminal pro-brain natriuretic peptide [mean difference (95% CI) 117 (−11, 245) and 92 (−30, 215) ng/l, respectively], and CMR-extracellular volume [mean (S.D.) 32 (2) *vs* 29 (4)%]. Late gadolinium enhancement was observed in five patients, only one with significant arrhythmia.

Conclusion. This first ILR study identified potentially life-threatening arrhythmias in asymptomatic SSc patients attributable to a primary SSc heart disease. Disease phenotype, CMR-extracellular volume (indicating diffuse fibrosis) and cardiac biomarkers may identify at-risk patients that would benefit from ILR screening. Future studies can inform a risk model and provide insights into SSc-associated arrhythmia pathogenesis.

Key words: SSc, SSc-heart disease, implantable loop recorder detected-arrhythmias, cardiovascular magnetic resonance (CMR), cardiovascular biomarkers

Rheumatology key messages

- This first implantable loop recorder (ILR) study identified incidental significant arrhythmias in asymptomatic SSc patients.
- Severe arrhythmias were detected in SSc patients with poor prognostic factors.
- Cardiovascular biomarkers and cardiovascular magnetic resonance-diffuse fibrosis may be useful for screening significant arrhythmia.

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CLINICAL SCIENCE

Introduction

Scleroderma heart disease (SHD) is associated with significant mortality, particularly from arrhythmias [1]. The underlying pathophysiology is distinct from atherosclerosis, with autopsy and cardiac magnetic resonance (CMR) studies demonstrating pathology in areas of the myocardium unrelated to coronary artery blood flow compromise [2, 3]. The hallmark of SHD is myocardial fibrosis, with or without myocardial inflammation [4], which may occur independently, or as a consequence of microvascular-perfusion abnormalities [5]. The pathophysiology of SHD-associated arrhythmias remains unclear, with fibrosis sparing the conduction pathway on autopsy studies, and not all patients with fibrosis developing clinically relevant arrhythmias [5, 6]. However, conduction abnormalities are more frequent in individuals with ischaemic heart disease (IHD), with fibrosis the principle underlying pathophysiological process of sudden cardiac death [7].

Most studies investigating SHD [8, 9] have not attempted to distinguish IHD from primary SHD. Standard electrophysiological (EP) monitoring methods only cover a limited period, and such studies have usually reported supraventricular and ventricular ectopics, which unless of high burden, are considered benign [9, 10]. The implantable loop recorder (ILR) used in the investigation of unexplained syncope, can record EP data for up to 3 years. The value of ILR to screen for significant arrhythmias in asymptomatic but high-risk SSc patients has not yet been evaluated. CMR imaging provides functional assessment, but also tissue characterization including detection of focal and diffuse fibrosis [4, 8] [through late gadolinium enhancement (LGE) and extracellular volume (ECV) quantification, respectively], and also microperfusion. The association between CMR findings and conduction abnormalities in SSc is not clear.

The primary objective of this electrophysiology and cardiac imaging in sclerodermA (ELCASA) study was to assess for significant primary SHD-related cardiac conduction abnormalities with the novel use of the ILR, and to identify disease phenotype, blood and CMR biomarkers that associate with significant arrhythmias.

Methods

Consecutive patients attending the specialist SSc clinic at the Leeds Teaching Hospitals NHS Trust were approached to enter this single centre 144-week-long prospective pilot study. Participants underwent a clinical evaluation and contrast-enhanced CMR followed by the insertion of an ILR. Participants were reviewed 3-monthly for 3 years. All patients gave their written informed consent to take part in the study with approval of the National Research Ethics Service (12/YH/0298). The study was conducted according to the Declaration of Helsinki.

Patients

All patients fulfilled the 2013 American College of Rheumatology/European League of Rheumatism criteria for SSc [11]. Participants were excluded if they had a prior diagnosis of primary SHD, traditional cardiovascular disease, diabetes or more than one traditional cardiovascular (CV) risk factor (defined as current smoker, hypertension, hypercholesterolaemia/hypertriglyceridaemia and family history of premature CV disease).

Clinical and serum sample collection

Demographic and clinical data, including traditional CV risk factors were recorded. Fasting lipid profile and glucose, creatine kinase, high-sensitivity cardiac troponin I (hs-TnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured (see Supplementary Methods, available at *Rheumatology* online).

CMR protocol

The CMR study was performed on a 3 T Philips Achieva MR system (Best, The Netherlands). The CMR protocol included LGE and T1 mapping for ECV quantification (to assess focal and diffuse fibrosis, respectively), myocardial perfusion, resting wall motion and left ventricular (LV) function, tissue tagging and aortic distensibility see Supplementary Methods, available at *Rheumatology* online).

ILR

The ILR (Medtronic Reveal XT, Dublin, Ireland) was implanted subcutaneously in a left pectoral position. The device was interrogated every 3 months for 3 years and if/when the patient was symptomatic.

Statistical analysis

As this was a first pilot study no formal power calculation was indicated.

The primary outcome was development of significant arrhythmia (defined as requiring a change in pharmacotherapy and/or insertion of anti-arrhythmic device). SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) was used for analysis. Descriptive analyses were undertaken, including an independent *t*-test for differences in those with and without significant arrhythmias. Spearman's test evaluated correlations between significant arrhythmias and CV biomarkers and continuous CMR measures.

Results

Twenty patients were recruited, of which 19 had ILR inserted and 15 of the 19 had CMR performed (Supplementary Fig. S1, available at *Rheumatology* online); of these 15 with a CMR, LGE and ECV data could be obtained from 14, and perfusion data from 12.

Baseline characteristics

Eleven patients (63%) were female, mean (S.D.) age of 53 (12) years, and median (interquartile range; IQR) disease duration of 7.5 (1.8, 19.5) years. Seven patients had dcSSc and eight had interstitial lung disease. No patient had a history of pulmonary hypertension. Six and five patients were ACA and anti-topoisomerase (Scl70) positive, respectively (Table 1 and Supplementary Table S1, available at *Rheumatology* online).

Table 1 Disease-specific characteristics of patients with SSc

Characteristic	SSc patients ($n = 19$)
Female, *n* (%)	12 (63)
Presence of RP, *n* (%)	19 (100)
Time since onset of RP, median (IQR), years	10.1 (2.4, 21.8)
Time since onset of first non-RP symptom, median (IQR), years	7.5 (1.8, 19.5)
History of, *n* (%)	
Digital ulceration	6 (32)
GORD	17 (90)
ILD	8 (42)
Palpitations	9 (47)
Standard of care tested cardio-pulmonary profile, mean (S.D.), %	
Forced vital capacity	92 (25)
Total lung capacity	92 (20)
DLCO	63 (16)
DLCO/VA	78 (17)
Electrocardiogram, *n* (%)	
Rhythm	19 (100) sinus rhythm
Axis	2 (11) LAD
Block	1 (5) incomplete RBBB, 1 (5) LBBB, 1 (5) left anterior fascicular block
LV ejection fraction % on echocardiogram, mean (S.D.)	56 (9)
RV–RA gradient on echocardiogram, mean (S.D.), mmHg[a]	22 (6) ($n = 12$)
CV risk profile	
Smoking status: never/ex/current, *n* (%)	8 (42)/11 (58)/0 (0)
Hypertension, *n* (%)	0 (0)
Hypercholesterolaemia, *n* (%)	0 (0)
FH premature CVD[b], *n* (%)	2 (11)
Serology and acute phase, *n* (%)	
ANA positive	18 (95)
ACA positive	6 (32)
Scl70 positive	5 (26)
CRP (normal range <5), median (IQR), mg/l	0 (0.0, 1.3)
Cardiovascular biomarkers and lipid profile	
hs-TnI, mean (S.D.), ng/l	76 (137)
NT-proBNP, mean (S.D.), ng/l	145 (130)
CK, mean (S.D.), IU/l	141 (148)
Glucose, mean (S.D.), mmol/l	4.8 (0.5)
Total cholesterol, mean (S.D.), mmol/l	4.9 (1.0)
HDL-C, mean (S.D.), mmol/l	1.5 (0.4)
LDL-C, mean (S.D.), mmol/l	2.8 (0.8)
TC/HDL-C ratio, mean (S.D.)	3.7 (1.3)
Triglycerides, mean (S.D.), mmol/l	1.6 (0.8)

[a]Many values missing due to poor tricuspid regurgitation/image quality. [b]Defined as first degree relative with a history of CVD when 60 years old or younger if female, and 55 years old or younger if male. CK: creatine kinase; CV: cardiovascular; CVD: cardiovascular disease; DLCO: diffusing capacity of the lungs for carbon monoxide; DLCO/VA: DLCO adjusted for volume; GORD: gastro-oesophageal reflux disease; FH: family history of; HDL-C: high density lipoprotein cholesterol; hs-TnI: high-sensitivity troponin I; ILD: interstitial lung disease; IQR: interquartile range; LAD: left axis deviation; LBBB: left bundle branch block; LDL-C: low density lipoprotein cholesterol; LV: left ventricular; NT-proBNP: N-terminal pro-brain natriuretic peptide; RBBB: right bundle branch block; RP: Raynaud's phenomenon; RV-RA: right ventricular-right atrial; Scl70: anti-topoisomerase antibody.

ILR findings

Over 3 years, the ILR detected findings in 13 (68%) participants, from benign to serious arrhythmias (Supplementary Table S2, available at *Rheumatology* online). Eight (42%) patients had significant arrhythmias: one had complete heart block (CHB); two had non-sustained ventricular tachycardia (NSVT); and five had atrial arrhythmias of which one had atrial flutter, one had atrial fibrillation (AF), one had supraventricular tachycardia (SVT) followed by AF, one had SVT, and one had atrial flutter followed by AF and SVT. Only one patient reported palpitations at the time of the arrhythmia (NSVT). The median (IQR) time from ILR implantation to significant arrhythmia was 12 (4.5, 24) months.

Of the eight SSc patients with significant arrhythmias, six were female, with mean (S.D.) age 55 (10) years and median (IQR) time from first non-Raynaud's phenomenon symptom 3.1 (20.1) years. All three patients with serious arrhythmias (NSVT/CHB) were dcSSc with interstitial lung disease, mean (S.D.) disease duration of 2 (1) years, two of them males with DU and also Scl70 positive. The other five patients with atrial arrhythmia were all ACA positive except one, only one was dcSSc, and one had a history of DU (Supplementary Table S3, available at *Rheumatology* online). There were no complications during the ILR implantation. One patient reported discomfort at the site of insertion and shoulder during the first year. This persisted post-ILR removal but with no evidence of infection or complication.

Baseline CV biomarkers and ILR-detected significant arrhythmias

hs-TnI and NT-proBNP were higher in the eight patients with significant arrhythmias compared with those without [mean difference (95% CI) 117 (−11, 245) and 92 (−30, 215) ng/l, respectively]. There was no difference in creatine kinase levels between the two groups (Table 2, Supplementary Fig. S2, available at *Rheumatology* online).

CMR and development of ILR-detected significant arrhythmias

CMR-ECV, indicative of diffuse fibrosis, was higher in those with significant arrhythmias compared with those without [mean difference (95% CI) 2 (−2, 6)%]. Although within normal range, a trend for greater LV ejection fraction and LV mass appeared in those with significant arrhythmias [mean difference (95% CI) 2 (−3, 8)% and 2 (−10, 15) g/m^2, respectively] (Table 2, Supplementary Table S4, available at *Rheumatology* online).

Five of the 14 patients with contrast-enhanced CMR imaging had evidence of focal fibrosis as evidenced by LGE; only 1/5 developed a significant arrhythmia (NSVT) with LGE present in the basal inferolateral midwall. Of the remaining four, one had transmural LGE in the basal inferolateral wall (ILR data available for year 1 only), two had LGE that was focal in nature and one had LGE that was diffuse in nature.

None of the 12 patients with perfusion CMR had visual perfusion defects. Quantitative assessment showed no differences in myocardial blood flow at rest or stress or myocardial perfusion reserve between those with and those without significant arrhythmias.

Baseline CV biomarkers and CMR

CMR-detected fibrosis in itself signifies SHD, albeit subclinical and with unclear clinical implication. Baseline hs-TnI and NT-proBNP were higher in patients with LGE [mean difference (95% CI) 91 (−14, 196) and 95 (−49, 239) ng/l, respectively] and negatively correlated with myocardial perfusion reserve ($r = -0.59$, $P = 0.053$ and $r = -0.74$, $P = 0.006$, respectively). There was a trend towards a positive correlation between hs-TnI and ECV ($r = 0.45$, $P = 0.125$) and negative correlation between hs-TnI and LV ejection fraction ($r = -0.39$, $P = 0.162$) (Supplementary Table S5, available at *Rheumatology* online).

Medical outcomes for participants

Six participants required medical treatment as a direct result of the study. The patient with CHB was immediately admitted for insertion of a permanent pacemaker. Beta-blockers were commenced for the patients with NSVT and atrial flutter followed by AF and SVT, with appropriate monitoring, and calcium channel blocker for the patient with SVT and AF. Anticoagulation was commenced in one patient with AF.

Table 2 Cardiac serum biomarker and CMR measures in study participants with significant arrhythmias compared with those without significant arrhythmias

	Significant arrhythmia on ILR ($n = 8$)	No significant arrhythmia on ILR ($n = 11$)	Mean difference (95% CI)
Cardiac serum biomarkers			
hs-TnI, ng/l	141 (184)	23 (51)	117 (−11, 245)
NT-proBNP, ng/l	198 (128)	106 (122)	92 (−30, 215)
CK, IU/l	152 (162)	133 (145)	19 (−138, 176)
CMR ($n = 15$)			
LGE present ($n = 5$)	1 (7)	4 (29)	
LGE not present ($n = 9$)	4 (29)	5 (36)	
ECV ($n = 14$)	32 (2)	29 (4)	2 (−2, 6)
MPR ($n = 12$)	1.9 (0.4)	2.1 (1.2)	−0.2 (−1.3, 0.8)
LVEF	62 (4)	59 (5)	2 (−3, 8)
LV mass/BSA, g/m^2	46 (7)	44 (14)	2 (−10, 15)

Mean (S.D.) values are shown unless stated otherwise. 15/19 patients had CMR performed. Of these 15 with a CMR, LGE and ECV data could be obtained from 14, and perfusion data from 12. BSA: body surface area; CK: creatine kinase; CMR: cardiovascular magnetic resonance; ECV: extracellular-volume fraction; hs-TnI: high-sensitivity troponin I; ILR: implantable loop recorder; LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; MPR: myocardial perfusion reserve; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Concomitant cardio-pulmonary co-morbidity and medication

Over the study period, no patients were diagnosed with pulmonary hypertension or ischaemic CV disease. Cyclophosphamide use in five patients appeared unrelated to development of arrhythmia, with one patient developing NSVT 1 year following cyclophosphamide treatment and another with SVT before.

Discussion

This is the first study to evaluate the use of ILR for the screening of incidental primary SHD-associated arrhythmias. Almost half the patients had a clinically significant arrhythmia, potentially life-threatening in three. ILR arrhythmias appeared to be associated with hs-TnI, NT-proBNP and CMR measure of diffuse rather than focal fibrosis; and incidentally, LGE also correlated with hs-TnI and NT-proBNP.

Patients with SSc may exhibit traditional IHD and/or primary SHD. Pathways to risk stratify and manage IHD are well-established. In contrast, optimal detection and management of primary SHD remains unclear. EP studies have relied on short period monitoring methods, with most including benign findings. There are no data on pre-emptive ILR use in an unselected general population, although, emerging data in other at-risk groups identify a significant proportion developing arrhythmias [12]. Our study excluded IHD, yet still detected significant arrhythmias, indicating underlying primary SHD aetiology.

The significant arrhythmias were detected over the course of 3 years, highlighting the limited value of short-term EP methods. Only one patient reported palpitations at the time of the arrhythmia, suggesting such history is of limited value. All three patients with more severe arrhythmias (CHB/NSVT) had early dcSSc and interstitial lung disease, two were Scl70 positive, two were males, reinforcing the association of SHD arrhythmias with SSc poor prognostic factors [13, 14].

In individuals with IHD, fibrosis is identified as the principal underlying pathophysiological process of sudden cardiac death [7]. Few studies have assessed the association between myocardial fibrosis and EP outcomes in SSc. Two studies of modest size found no association [6, 15], whereas another study identified abnormal Holter monitoring with greater burden of myocardial LGE [2]. In our study only one of the five patients with LGE had significant arrhythmia (NSVT). The location and extent of myocardial LGE are likely of relevance as both have been associated with arrhythmias and sudden cardiac death in cardiomyopathies [16, 17]. Quantitative LGE in our study revealed low scar mass values, possibly explaining the absence of association between LGE and arrhythmias.

This study was a first for evaluating association of CMR-ECV (a sensitive and quantitative measure of fibrosis) with arrhythmia. Given the strong association of myocardial fibrosis in autopsy studies with arrhythmias [5], and in our study, the association of diffuse (but not LGE focal) fibrosis with arrhythmia, burden of fibrosis may be relevant.

Five arrhythmias were supraventricular, occurring in females, four ACA positive and only one with dcSSc. None had common CV causes, implying SHD as the underlying cause. Further study is required to confirm whether there is an association of lcSSc with atrial arrhythmias, although detection of atrial fibrosis on CMR is challenging.

Serum CV biomarkers, hs-TnI and NT-proBNP, are sensitive tools in the detection of cardiac pathology in the general population, and in SSc [18, 19]. To our knowledge, ours is the first study to associate primary SHD arrhythmias with hs-TnI and NT-proBNP, implicating myocardial injury. The mechanism of myocardial damage is not clear but may reflect microvascular myocardial impairment as a consequence of endothelial dysfunction and subsequent scarring. Finally, this study also showed an association of hs-TnI and NT-proBNP with the CMR measures of fibrosis and myocardial perfusion reserve. Whilst indicating a subclinical cardiomyopathy, these biomarkers may have predictive utility in the identification of future clinical SHD.

Cyclophosphamide, notably high dose, is associated with cardiotoxicity [20]; however, of two patients receiving cyclophosphamide in our study, there was no temporal association with the development of arrhythmia.

The main limitation of our study is its modest size. However, this is a first, pilot study in a rare disease that has demonstrated the feasibility and utility of the ILR in asymptomatic individuals. A larger study is warranted to validate the initial findings and establish a risk model to inform ILR use in clinical practice.

In summary, this ELCASA study demonstrated ILR-detected incidental significant arrhythmias in asymptomatic patients. Together with known SSc poor prognostic factors, this study indicates that CMR-ECV and CV biomarkers could provide a basis for more refined screening algorithms and pre-emptive ILR insertion in the at-risk patient. Finally, the study provides valuable insights into SHD pathogenesis, suggesting an association between arrhythmias and fibrosis.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Tyndall AJ, Bannert B, Vonk M *et al*. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809–15.

2 Tzelepis GE, Kelekis NL, Plastiras SC *et al*. Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed enhanced magnetic resonance imaging study. Arthritis Rheum 2007;56:3827–36.

3 Hachulla AL, Launay D, Gaxotte V *et al*. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. Ann Rheum Dis 2009;68:1878–84.

4 Ntusi NA, Piechnik SK, Francis JM *et al*. Subclinical myocardial inflammation and diffuse fibrosis are common in systemic sclerosis—a clinical study using myocardial T1-mapping and extracellular volume quantification. J Cardiovasc Magn Reson 2014;16:21.

5 Bulkley BH, Ridolfi RL, Salyer WR, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976;53:483–90.

6 Rodriguez-Reyna TS, Morelos-Guzman M, Hernandez-Reyes P *et al*. Assessment of myocardial fibrosis and microvascular damage in systemic sclerosis by magnetic resonance imaging and coronary angiotomography. Rheumatology (Oxford) 2015;54:647–54.

7 Kuruvilla S, Adenaw N, Katwal AB *et al*. Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: a systematic review and meta-analysis. Circ Cardiovasc Imaging 2014;7:250–8.

8 Hachulla AL, Launay D, Gaxotte V *et al*. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. Ann Rheum Dis 2009;68:1878–84.

9 Nordin A, Bjornadal L, Larsson A, Svenungsson E, Jensen-Urstad K. Electrocardiography in 110 patients with systemic sclerosis: a cross-sectional comparison with population-based controls. Scand J Rheumatol 2014;43:221–5.

10 Kostis JB, Seibold JR, Turkevich D *et al*. Prognostic importance of cardiac arrhythmias in systemic sclerosis. Am J Med 1988;84:1007–15.

11 van den Hoogen F, Khanna D, Fransen J *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747–55.

12 Sacher F, Jesel L, Borni-Duval C *et al*. Cardiac rhythm disturbances in hemodialysis patients: early detection using an implantable loop recorder and correlation with biological and dialysis parameters. JACC Clin Electrophysiol 2018;4:397–408.

13 Allanore Y, Meune C, Vonk MC *et al*. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. Ann Rheum Dis 2010;69:218–21.

14 Hunzelmann N, Genth E, Krieg T *et al*. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. Rheumatology (Oxford) 2008;47:1185–92.

15 Muresan L, Oancea I, Mada RO *et al*. Relationship between ventricular arrhythmias, conduction disorders, and myocardial fibrosis in patients with systemic sclerosis. J Clin Rheumatol 2018;24:25–33.

16 Leyva F, Taylor RJ, Foley PW *et al*. Left ventricular midwall fibrosis as a predictor of mortality and morbidity after cardiac resynchronization therapy in patients with nonischemic cardiomyopathy. J Am Coll Cardiol 2012;60:1659–67.

17 Dweck MR, Joshi S, Murigu T *et al*. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58:1271–9.

18 Avouac J, Meune C, Chenevier-Gobeaux C *et al*. Cardiac biomarkers in systemic sclerosis: contribution of high-sensitivity cardiac troponin in addition to N-terminal pro-brain natriuretic peptide. Arthritis Care Res 2015;67:1022–30.

19 Nordin A, Svenungsson E, Bjornadal L *et al*. Troponin I and echocardiography in patients with systemic sclerosis and matched population controls. Scand J Rheumatol 2017;46:226–35.

20 Dhesi S, Chu MP, Blevins G *et al*. Cyclophosphamide-induced cardiomyopathy: a case report, review, and recommendations for management. J Investig Med High Impact Case Rep 2013;1:232470961348034.