



UNIVERSITY OF LEEDS

This is a repository copy of *Primary myocardial disease in scleroderma – a comprehensive review of the literature to inform the UK Systemic Sclerosis Study Group cardiac working group*.

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/106112/>

Version: Accepted Version

Article:

Bissell, L-A orcid.org/0000-0002-2789-4652, Md Yusof, MY orcid.org/0000-0003-3131-9121 and Buch, MH orcid.org/0000-0002-8962-5642 (2017)
Primary myocardial disease in scleroderma – a comprehensive review of the literature to inform the UK Systemic Sclerosis Study Group cardiac working group. *Rheumatology*, 56 (6). pp. 882-895. ISSN 1462-0324

<https://doi.org/10.1093/rheumatology/kew364>

© The Author 2016. Published by Oxford University Press on behalf of the British Society for Rheumatology.

Reuse

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Supplementary data

Table S1: Electrophysiology studies describing cardiac abnormalities in Systemic Sclerosis.

Reference	Study population	n	ACR met	% female	Lc/DcSSc	Age, years mean (SD)	Disease duration, years mean (SD)	Procedure	Results
Ciftci [1] 2007	Turkey	60; free of CVD and CV RFs	yes		16 (27%)/44 (73%)	46(11) dcSSc, 650(12) lcSSc	7.6 (7) (not defined)	24 hour ambulatory monitor, echo	HRV: SDNN decreased in dcSSc vs. lcSSc/controls (p=0.01), no correlation with disease duration, mRSS, RP.
Draeger [2] 2011	USA	265	or 3 CREST features met	75	NR	48.8 Females, 48.0 males	2.5 (from 1 st non RP symptom)	ECG	2.6% sinus tachycardia, 7.2% sinus bradycardia, 5.3% first degree AV block, 7.6% fascicular block, ECG findings not associated with disease type/autoantibody. Survival analysis: over 9 years average follow-up, patients with fascicular block at increased risk of mortality (HR: 2.3; 95% CI:1.1, 4.6, p=0.02), after adjustment for age at enrolment. In the multivariable model, the predictive significance of fascicular blocks for survival was independent of non-SSc related cardiac risk factors (HR: 2.1; 95% CI: 1.02, 4.28, p=0.04).
Follansbee [3] 1985	USA	102; cardiac disease in 19% of dc and 16% of lcSSc	88%	80	49(48)/53(52)	51 (13)	7.6 (8.1) (not defined)	ECG	51% abn. ECG; 14% ST-T wave changes, 8% prolonged PR, 10% left anterior fascicular block, 3% non-significant IV conduction abn, 1% high grade AV block, 10% prolonged QRS: normal ECG associated with normal LV function on echo
Nordin [4] 2014	Sweden	110; 12% IHD, 2% PPM, 5% LVEF<50% 105 controls	yes	81	86 (78)/23 (22)	62 (12)	9.4 (range 5.6-17) (not defined)	ECG, 49 underwent 24 hour ambulatory monitor	28% abn. ECG, (17% controls, p =0.05) 15% AV/IV conduction abn. (5% controls, p<0.01). All with normal ECG had LVEF>50%. ECG abn. not associated with serology, CRP, subtype, organ involvement or disease duration. Ambulatory results: 38% SSc 17% controls abn, p0.05; mainly extra systoles; 2 patients had short SVTs, mean and lowest HR higher in SSc

Kostis [5] 1988	USA	183 Free of CVD	yes	79	45 (25)/104 (57)	49 (13)	NR	ECG, 24 hour ambulat ory monitor	43% abn ECG (31% ns ST-T changes, 20% conduction defect). Holter:61% PACs, 21%SVT, 4% long PR interval, 1% each; Wenckebach, bradycardia and CHB, 67% PVCs, 9% >1000PVCs/24hrs, 7% VT. Generalised disease more likely to have SVT, VT and PVCs, and those with abn. ECG, pulmonary involvement, FEV1<70% and loud S2 more likely to have abn. on holter. MVA : cardiac arrhythmias ass. with mortality independent of increasing age, ILD, GORD etc.
Morelli [6]	Italy	77 free of IHD 33 controls	yes	88	35 (45)/42 (55)	50 (13)	10.3 (5) (from RP onset)	ECG, 24 hour holter, echo, SAE, resting myocardi al scintigra phy	20.5% had LVP vs. 3% controls (p=0.02). 14/15 SSc pts with LVP had abnormal myocardial scintigraphy vs. 29/58 without LVP (p=0.002). SSc patients with LVP more likely to have abn. myocardial scintigraphy (p=0.002). No association of LVP found with age, sex, disease duration, ILD or complex arrhythmias. LVP more in dcSSc than lcSSc (30% vs. 9% respectively, p=0.04).
Urai [7] 1978	Hungary	193	Pre 1980	87	NR	48	NR	ECG, echo	43 (23%) had IVCD; most frequently left anterior hemiblock (3.4% of 193 patients) 96 followed up over average time of 9.4 years; 30% of patients showed evidence of new IVCD. 47% of those with IVCD developed AV block/other rhythm disturbances Septal hypertrophy more likely in those with IVCD

Abn., abnormal; AV, atrioventricular; CHB, complete heart block; CI, confidence interval; CRP, C-reactive protein; dcSSc, diffuse cutaneous SSc; ECG, electrocardiogram; GORD, gastro-oesophageal reflux disease; HR, Hazard ratio; HRV, heart rate variability; ILD, interstitial lung disease; IV, interventricular; IVCD, IV conduction disturbance; lcSSc, limited cutaneous SSc; LV, left ventricular; LVP, late ventricular potential; mRSS, modified Rodnan skin score; MVA, multi-variate analysis; NR, not reported; PVC, premature ventricular complex; RP, Raynaud's phenomenon; SD, standard deviation; SSc, Systemic Sclerosis; SVT, supraventricular tachycardia; VT, ventricular tachycardia

Table S2: Echocardiography studies describing cardiac abnormalities in Systemic Sclerosis.

Reference	Study population	n	Relevant pt features	% female	Lc/DcSSc %	Age, years, mean (SD)	Disease duration, years, mean (SD)	Results
Aguglia [8] 2001	Italy	124 41 controls	Unselected	85	54/46	52.0 (12.5)	11.2 (8.0) (not defined)	Mean (SD) LVEF 62 (7)% LVSD 7% Mean (SD) E/A ratio 1.1 (0.5) (p=0.05 vs controls) 44.4% inverted E/A ratio PASP > 45mmHg 36%* LVH 32%* Moderate or severe pericardial effusion 5%* Valvular heart disease 4%* *Conditions noted to affect diastolic function; without these conditions including chronic renal insufficiency, arterial hypertension, coronary heart disease; no difference between SSc patients and controls found for BP, LVEF, LV mass and Doppler variables for diastolic dysfunction (including E/A ratio)
Allanore [9] 2009	France	69	No hx of PAH	81	52/48	56.1 (12.6)	8.7 (8.4) (not defined)	Mean (SD) LVEF 65 (6)%, E/A ratio 1(0.3) PAP 24.7 (6.3)mmHg 7% pericardial effusion 19% myocardial involvement (defined as depressed contractility of ventricles or presence of diastolic HF)
Allanore [10] 2010	EUSTAR	7073	Unselected	86	70/30	56 (14)	9.7 (not defined)	LVEF<55%: 5.4%: independently associated with age, male gender, myositis, digital ulcers, lung involvement and absence of previous treatment with calcium channel blockers.
Candell-Reira [11]	Spain	63, 40 controls	Unselected	81	100/0	54 (12)	17 (11) (not defined)	Mean (SD) Mitral E/a ratio 1.02 (0.3), p=0.0013 vs. controls, adjusted for hypertension, heart rate, age, mitral regurgitation, and pericardial effusion. 18% Pericardial effusion 49% MR 30%TR 14% PASP> 40mmHg
De Groote [12] 2008	France	570	No hx of PFT abnormalitie	85	74/26	54 (13)	9 (8)*	Mean (SD) LVEF 65 (8)%, E/A ratio 1.1 (0.4) – all no difference between dc or lcSSc 23% LVH

			s, severe cardiac disease or PAH					18% LV diastolic dysfunction MR: Grade III–IV: 0.4%, II: 6.7%, AR: Grade III–IV: 0%, II: 2.5% Aortic stenosis: 3.3% 3.2% PASP > 40mmHg
Hegedus [13] 1993	Hungary	80 18 age/sex matched controls	74% had lung involvement	90	71/29	50.1 (12.5)	9 (8) (not defined)	Mean (SD) LVEF 45.2 (9.5)% LVEF and stroke volume lower vs. controls, but no differences detected in LVESD or LVEDD between SSc vs. controls 19% LVH Pericardial thickening (>7 mm) was 18%, pericardial effusion 11%
Hinchcliff [14] 2012	USA	153	17 had PAH, 5 IHD	85	60/40	51 (13)	Not given for whole cohort	5.2% had abnormal LVEF (<55%) 5.2% had LVSD 23% diastolic dysfunction During a mean follow-up of 1.9+/-1.3 years, LV diastolic dysfunction independently associated with increased risk of death (HR 3.2, 95% CI 1.1-9.5, p=0.034 per each SD decrease in tissue Doppler E' velocity)
Maione [15] 2005	Italy	77 45 controls	40% known heart involvement	92	25/22	54.4 ± 10.9	18.2 ± 9.2 (from RP onset)	Mean (SD) LVEF 59.6 (6)% 1.3% abnormal LVEF (<55%) 7.9% LVH (p=0.002 vs. controls) 14% pericardial effusion (P<0.001 vs controls) 40% valvular heart disease (p<0.001 vs controls) 37% inverted E/A ratio Mean (SD) E/A ratio 1.08 (0.37) (p<0.001 vs controls)
Meune [16] 2008	France	100 26 controls	Unselected	86	58/42	53.7 ± 13.9	7.9 ± 7.9 (not defined)	15% pericardial effusion, 45% valvular heart disease; (p=ns vs controls for both) Mean (SD) LVEF 64.9 (0.6)%, 7% abnormal LVEF (<55%) (p=ns) 14% LVSD 50% diastolic dysfunction 30% inverted E/A ratio Mean (SD) E/A ratio 1.0 (0.3) (p=0.038 vs controls) 11% had mean PASP>40mmHg (p=ns vs controls)
Minier [17] 2010	Hungary	131	Unselected	90	69/31	55.9 (SD11.7)	8.1 (SD7.2)*	3.1% LVEF≤50% 52% diastolic dysfunction
Morelli [18] 1996	Italy	72 64 controls	No evidence of heart disease	86	40/60		10 (from RP onset)	49% cardiac involvement 22.2 % LVH (p=0.013 vs controls) 5.5% pericardial effusion (p=ns vs controls) 8.3% valvular heart disease (p=ns vs controls)

								Mean (SD) PASP 40.99 (16.37)mmHg (p<0.001 vs controls)
Murata [19] 1998	Japan	95	18 had PAH	91	67/37	NR for whole cohort	NR for whole cohort	31% cardiac involvement 12.6% LVH 7.4% cardiomyopathy 8.4% valvular heart disease
Plazak [20] 2011	Poland	60 30 controls	Unselected	90	55/45	51.8	15.5 (not defined)	63.3% cardiac involvement 3.3% LVH (p=ns vs controls) 13.3% pericardial effusion (p<0.01 vs controls) 11.7% valvular heart disease (p<0.01 vs controls) 3.3% abnormal LVEF (<55%) (p=ns vs controls) 63.3% diastolic dysfunction 63.3% inverted E/A ratio Mean (SD) E/A ratio 0.98 (0.3) (p<0.001 vs controls) 10% had mean PASP>40mmHg (p<0.01 vs controls)
Poormoghim [21]	Iran	58	Unselected	91	60/40	40.9 (13.7)	7.3 (8.5) dcSSc, 8.4 (8.2) lcSSc (from symptom onset)	15.5% pericardial effusion (moderate to severe in 5.1%)
Rosato [22] 2009	Italy	67	free of cardiac symptoms	90	55/45	52 (11)	15 (11) RP duration	6% pericardial effusion Mean (SD) LVEF 58.3 (2.4)% 36% inverted E/A ratio Mean (SD) E/A ratio 1.2 (0.49)
Schade [23] 2012	Brazil	87	Unselected	92	78/22	48.5 (11.7)	NR	4.6% abnormal LVEF
Yiu [24] 2011	Netherlands	104 37 controls	free of IHD 4% PAH	77	51/49	54 (12)	8.6 (6.3) from RP onset	Mean (SD) LVEF 63.5 (7.2)% (p=ns vs controls) 66% diastolic dysfunction (p<0.01 vs controls) Mean (SD) PASP 28.9 (8.7)mmHg (p<0.01 vs controls)

* From first non-RP symptom

AR, aortic regurgitation; BP, blood pressure; CI, confidence intervals; dcSSc, diffuse cutaneous SSc; E/A; early to late filling peak velocity ratio of tricuspid valve; HF, heart failure; HR, Hazard ratio; lcSSc, limited cutaneous SSc; LV, left ventricular; LVEF; left ventricular ejection fraction; LVESD, LV end systolic diameter; LVEDD, LV end diastolic diameter; LVH, LV hypertrophy; LVSD, LV systolic dysfunction; MR, mitral regurgitation; ns, non-significant; PAH, pulmonary hypertension; PAP, pulmonary arterial pressure; PASP, pulmonary arterial systolic pressure; RP, Raynaud's phenomenon; SD, standard deviation; SSc, Systemic Sclerosis; TR, tricuspid regurgitation.

Table S3: Cardiac magnetic resonance imaging studies describing cardiac abnormalities in Systemic Sclerosis.

Reference	Study population	n	Controls, n	ACR met	% female	Lc/DcSSc %	Age, years, mean (SD)	Disease duration, years, mean (SD)	CMR scan	Results
Bezante [25]2007	Italy	50 free of CVD	31 age/sex/BSA matched	Yes	90	66/34	53.3 (12.9)	12.2 (10.2) (from RP onset)	1.5T CMR	Mean LVEF/BSA 36.4% (38.6% in controls, p=0.009) Mean RVEF/BSA 28.1% (24.5% in controls, p<0.0001) RVEF worse in lcSSc vs. dcSSc (p=0.03) E/A lower in SSc (1.2 (0.29)) vs controls (1.35 (0.1))(p0.01)
Carmona-Henryon [26]* 2011	France	46	16	Not stated	NR	NR	NR	NR	DE-CMR	Shorter T1 in septal wall in SSc (345 vs. 360ms in controls, p=0.03). Systolic & early diastolic SR strain rate correlated with T1 (p<0.01)
Gargani [27]* 2012	Italy	53	N/A	Not stated	95	66/34	52 (14)	NR	DE-CMR and TDI echo	Non-ischaemic myocardial fibrosis in 23% Myocardial oedema: in 4% - resolved after steroid Mitral annulus E/E' ratio independent predictor of fibrosis (HR 1.8 (95CI:1.1-3.1)), but no association of fibrosis with disease subtype, duration or age.
Hachulla [28] 2009	France	52	N/A	Yes	85	64/36	56 (11)	6.6 (6.1) (from first non-RP symptom)	1.5T DE-CMR with contrast	Myocardial oedema in 12% Myocardial thinning in 29% Pericardial effusion in 19% Mean RVEF 34%: 21% impaired Mean LVEF 48%: 23% impaired: worse in lcSSc vs. dcSSc (34% vs. 5%, p=0.02) DE abn. in 21%: mainly linear, midwall and rarely subendocardial, and no correlation with coronary artery distribution; worse with increasing disease duration (r=0.30, p<0.05)

Nassenstein [29] 2008	Germany	35 free of IHD	34 age/sex /CV RFs matched	yes	88	43/57	54 (14)	8.4 (7.4) (not defined)	1.5T DE-CMR	Mean LVEF 61.5% (63.3% in controls, p=ns); 21% LVEF<55% 15% abn. DE (3% in controls, p=ns); patchy areas in mid-myocardial layer; 1 patient with sub-endocardial layer involvement; mainly in left basal segment of LV; associated with abn. ECG and valvular pathologies, but not age, disease duration and mRSS. Number of segments with LGE higher in SSc vs. controls (p<0.005) No myocardial oedema seen.
Rodriguez-Reyna* [30] 2011	Mexico	62	N/A	NR	97	53/47	NR	9.7	CMR & stress perfusion	Mean LVEF 59.4% Subendocardic perfusion defects in 79% (correlated with high CRP, p=0.001) DE abn. in 45% (18% patchy, 36% bands, 11% subendocardic, 29% mixed, 7% transmural); worse in dcSSc (58.6 vs. 33.3% lcSSc, p=0.04), mainly in basal anteroseptal and inferoseptal segments. Fibrosis correlated with LVEF (p<0.0009)
Tzelepis [31] 2007	Greece	36 free of IHD or CV RFs	N/A	Yes	89	36/64	NR	Not given	1.5T DE-CMR	DE abn. in 66%; mainly midwall, and linear, sparing subendocardial layer, in basal and mid-cavity segments of LV; greater no. of enhancing segments in RP>15yrs (p=0.017) and those with abn. 24 hr ECG (p=0.035) but no association with disease subtype, PFTS or mRSS.

*Abstract publication

Abn., abnormal; BSA, body/surface index; CI, confidence interval; CMR, cardiac magnetic resonance; CV, cardiovascular; CVD, cardiovascular disease; dcSSc, diffuse cutaneous SSc; DE-CMR, delayed enhancement CMR; E/A; early to late filling peak velocity ratio of tricuspid valve; ECG, electrocardiogram; HR, Hazard ratio; IHD, ischaemic heart disease; lcSSc, limited cutaneous SSc; LGE, late gadolinium enhancement; LV, left ventricular; LVEF; left ventricular ejection fraction; mRSS, modified Rodnan skin score; NR, not reported; PFTs, pulmonary function tests; RFs, risk factors; RVEF, right ventricular ejection fraction; RP, Raynaud's phenomenon; SD, standard deviation; SSc, Systemic Sclerosis

Table S4: Case studies describing the prevalence and nature of cardiac disease across serological subtypes in Systemic Sclerosis.

Reference	Study population	n	1980 ACR/LeRoy met	Anti-body, n (%)				Female %	Age, years~	Disease duration, years~	Cardiac involvement	
				ANA	ACA	ScI70	Others				Definition	%
Jacobsen [32]	Denmark	230	yes	196 (85)	78 (34)	30 (13)	15 (6.5) Anti-U1 RNP 8 (3.5) Anti-U3 RNP 5 (2.2) Anti-Th RNP	82	59 (46, 86)~~	11 (5, 19)~~ from first SSc related symptom	Clinical or ECG abnormalities in the absences of other causes	ACA: 5 ScI70: 10 Anti-U1 RNP: 0 Anti-U3 RNP: 0 Anti-Th RNP: 0 ANA -ve: 11 P=ns vs. Ab and ANA negative
Denton [33]	UK	1966	yes	1654	618	683	Anti- RNA poly III: 77 Anti-U1 RNP: 102 Anti-U3 RNP: 38	82	54.2 (14.1)	NR	Not defined	ANA: 10.9 ACA: 9.1 ScI70: 12.4 Anti- RNA poly III: 6.4 Anti-U1 RNP: 11.8 Anti-U3 RNP: 13.2 No difference between groups
Ceribelli [34]	Italy	216	yes	NR	67 (31)	81 (38)	Anti-Th/To: 8 (4)	F:M ratio ACA: 66.1 Anti-Th/To 5.3	ACA: 66.6 (10.1) Anti-Th/To 54.5 (17.9)	ACA: 8.7 (5.9) Anti-Th/To 8.5 (6.5) (not defined)	Pericarditis	ACA: 4.5 Anti-Th/To: 25 p=0.028 between groups
de Souza Muller [35]	Brazil	85	y	93	26 (31)	27 (32)	Anti- RNA poly III: 35 (41)	92	ACA: 54.6 (10.5) ScI70: 45.8 (12.5)	ACA: 23 ScI70: 7 Anti- RNA poly III: 10 (not defined)	Palpitations	ACA: 35, ScI70: 15, Anti- RNA poly III: 20, p=0.07 across groups

									Anti- RNA poly III: 47.2 (12.8)		Cardiac conduction blocks Reduced LVEF Diastolic dysfunction	ACA: 24, Scl70: 4, Anti- RNA poly III: 9, p=0.05 across groups ACA: 8, Scl70: 4, Anti- RNA poly III: 12, p=ns across groups ACA: 38, Scl70: 28, Anti- RNA poly III: 33, p=ns across groups
Steen [36]	USA	963	yes		291 (30)	318 (33)	RNA poly III: 120 (12.5) Anti-U1 RNP: 71 (7.4) Anti-U3 RNP: 55 (5.7) PmScl: 36 (3.7) Anti-Th/To: 72 (7.5)	ACA: 92 Scl70: 73 RNA poly III: 81 Anti-U1 RNP: 79 Anti-U3 RNP: 71 PmScl: 81 Anti-Th/To: 81	NR	ACA: 20 Scl70: 16.3 RNA poly III: 11.3 Anti-U1 RNP: 16.5 Anti-U3 RNP: 12.0 PmScl: 14.3 Anti-Th/To: 16.3 (not defined)	Severe heart involvement reported only: cardiomyopathy with decrease in LVEF and symptoms of CCF, symptomatic pericarditis (pericardial pain) or cardiac decompensation from effusion, or arrhythmia attributable to SSc requiring Rx	ACA: 4 Scl70: 16 RNA poly III: 7 Anti-U1 RNP: 11 Anti-U3 RNP: 18 PmScl: 6 Anti-Th/To: 7, p<0.01 by ANOVA for Anti-U3 RNP and Scl70
Rodriguez -Reyna [37]	Mexico	139	84%	139 (100)	41 (30)	39 (28)	RNA poly III: 2 (1) Anti-U1 RNP: 15 (11)	93.5	45 (14.2)	NR	Left sided congestive heart failure (FEV1<45%) or pericarditis on	Anti-Ku 50% vs. 7% if anti-Ku -ve, p=0.04

								Anti-U3 RNP: 90 Anti-Ku: 100 Anti-Th: 80	Anti-U3 RNP: 36 (10) Anti-Ku: 30 (9) Anti-Th: 38 (13)			
Hanke [41]	Germany	280	Not all - DNSS study		NR	67 (24)	NR	F:M ratio 243:37	56 (13.2)	7 (7.38) from diagnosis	2 of the following symptoms: diastolic dysfunction, conduction abnormalities, cardiomyopathy, or reduced LVEF unrelated to other diseases, valvular changes not explained by other, or pericarditis. Abnormal ECG Conduction disturbance	49% vs. 38% Scl70 - ve, p=ns 41% vs. 22% Scl70 - ve, p=0.007 37% vs. 21% Scl70 - ve, p=0.009
Aggarwal[42]	USA	2579	81%	NR	NR	NR	Anti-U3 RNP: 108 (4)	Anti-U3 RNP: +ve: 71 -ve: 81	Anti-U3 RNP: +ve: 45.2 (15.6) -ve: 50.2 (14.3)	Anti-U3 RNP: +ve:5.3 (7.6) -ve:7.6 (9.4) from symptom onset	Any one of: left-sided congestive heart failure (clinical or estimated LVEF< 45%), pericarditis (pericardial pain plus pericardial friction rub, pericardial effusion, or ECG evidence of pericarditis).	23% vs. 20% Anti-U3 RNP negative, p=ns

												arrhythmia requiring treatment, CHB, or CTD-related cardiac cause of death.	
--	--	--	--	--	--	--	--	--	--	--	--	---	--

[~values indicate mean \(SD\) unless otherwise stated](#)

[~~median \(IQR\)](#)

[Ab, antibody; ACA, anti-centromere antibody; CCF, congestive cardiac failure; CTD, connective tissue disease; dcSSc, ECG, electrocardiogram; LV, left ventricular; LVEF, LV ejection fraction; NR, not reported; ns, non-significant; Scl70, anti-topoisomerase antibody; SD, standard deviation; SSc, Systemic Sclerosis; +ve, positive; -ve, negative.](#)

References

- 1 Ciftci O, Onat AM, Yavuz B, et al. Cardiac repolarization abnormalities and increased sympathetic activity in scleroderma. *J. Natl. Med. Assoc.* 2007;99(3):232-7.
- 2 Draeger HT, Assassi S, Sharif R, et al. Fascicular Block: A Predictor of Mortality In Early Systemic Sclerosis. *Arthritis Rheum.* 2011;63(10):S578-S.
- 3 Follansbee WP, Curtiss EI, Rahko PS, et al. The electrocardiogram in systemic sclerosis (scleroderma). Study of 102 consecutive cases with functional correlations and review of the literature. *Am. J. Med.* 1985;79(2):183-92.
- 4 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(3):221-5.
- 5 Kostis JB, Seibold JR, Turkevich D, et al. Prognostic importance of cardiac arrhythmias in systemic sclerosis. *Am. J. Med.* 1988;84(6):1007-15.
- 6 Morelli S, Sgreccia A, De Marzio P, et al. Noninvasive assessment of myocardial involvement in patients with systemic sclerosis: Role of signal averaged electrocardiography. *Journal of Rheumatology* 1997;24(12):2358-63.
- 7 Urai L, Veress G, Urai K. Scleroderma-heart and conduction disturbances. *Acta Med. Acad. Sci. Hung.* 1978;35(3-4):189-200.
- 8 Aguglia G, Sgreccia A, Bernardo ML, et al. Left ventricular diastolic function in systemic sclerosis. *J. Rheumatol.* 2001;28(7):1563-7.
- 9 Allanore Y, Wahbi K, Borderie D, Weber S, Kahan A, Meune C. N-terminal pro-brain natriuretic peptide in systemic sclerosis: a new cornerstone of cardiovascular assessment? *Ann. Rheum. Dis.* 2009;68(12):1885-9.
- 10 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(1):218-21.
- 11 Candell-Riera J, Armadans-Gil L, Simeon CP, et al. Comprehensive noninvasive assessment of cardiac involvement in limited systemic sclerosis. *Arthritis Rheum.* 1996;39(7):1138-45.
- 12 de Groote P, Gressin V, Hachulla E, et al. Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis. *Ann. Rheum. Dis.* 2008;67(1):31-6.
- 13 Hegedus I, Czirjak L. Left ventricular wall thickness and disease duration in systemic sclerosis. *Postgrad. Med. J.* 1993;69(810):285-90.
- 14 Hinchcliff M, Desai CS, Varga J, Shah SJ. Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. *Clin. Exp. Rheumatol.* 2012;30(2 Suppl 71):S30-7.

- 15 Maione S, Cuomo G, Giunta A, et al. Echocardiographic alterations in systemic sclerosis: a longitudinal study. *Semin. Arthritis Rheum.* 2005;34(5):721-7.
- 16 Meune C, Avouac J, Wahbi K, et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: A controlled study of 100 consecutive patients. *Arthritis Rheum.* 2008;58(6):1803-9.
- 17 Minier T, Nagy Z, Balint Z, et al. Construct validity evaluation of the European Scleroderma Study Group activity index, and investigation of possible new disease activity markers in systemic sclerosis. *Rheumatology* 2010;49(6):1133-45.
- 18 Morelli S, Sgreccia A, Ferrante L, et al. Relationships between electrocardiographic and echocardiographic findings in systemic sclerosis (scleroderma). *Int. J. Cardiol.* 1996;57(2):151-60.
- 19 Murata I, Takenaka K, Shinohara S, Suzuki T, Sasaki T, Yamamoto K. Diversity of myocardial involvement in systemic sclerosis: an 8-year study of 95 Japanese patients. *Am. Heart J.* 1998;135(6 Pt 1):960-9.
- 20 Plazak W, Kopec G, Tomkiewicz-Pajak L, et al. Heart structure and function in patients with generalized autoimmune diseases: echocardiography with tissue Doppler study. *Acta Cardiol.* 2011;66(2):159-65.
- 21 Poormoghim H, Poorkarim MA, Lakeh MM, Heshmati BN, Almasi S, Hakim M. Preliminary study of cardiovascular manifestations and cardiac severity scale in 58 patients with systemic sclerosis in Iran using the Medsger scale. *Journal of Tehran University Heart Center* 2010;5(1):14-8.
- 22 Rosato E, Maione S, Vitarelli A, et al. Regional diastolic function by tissue Doppler echocardiography in systemic sclerosis: correlation with clinical variables. *Rheumatol. Int.* 2009;29(8):913-9.
- 23 Schade L, Paiva ES, Muller CS. Skeletal and heart muscle involvement in SSc. *Rheumatology* 2012;51:ii61.
- 24 Yiu KH, Schouffoer AA, Marsan NA, et al. Left ventricular dysfunction assessed by speckle-tracking strain analysis in patients with systemic sclerosis: Relationship to functional capacity and ventricular arrhythmias. *Arthritis Rheum.* 2011;63(12):3969-78.
- 25 Bezante GP, Rollando D, Sessarego M, et al. Cardiac magnetic resonance imaging detects subclinical right ventricular impairment in systemic sclerosis. *J. Rheumatol.* 2007;34(12):2431-7.
- 26 Carmona-Henryon C, Thuny F, Schnell F, et al. Pathophysiology of asymptomatic left ventricular dysfunction in systemic sclerosis. *Eur. Heart J.* 2011;32:916.
- 27 Gargani L, Pingitore A, De Marchi D, et al. Cardiac involvement in SSc: The added value of magnetic resonance imaging. *Rheumatology* 2012;51:ii91.
- 28 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(12):1878-84.
- 29 Nassenstein K, Breuckmann F, Huger M, et al. Detection of myocardial fibrosis in systemic sclerosis by contrast-enhanced magnetic resonance imaging. *Rofo* 2008(12):1054-60. <http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/727/CN-00680727/frame.html>.
- 30 Rodriguez-Reyna TS, Morelos-Guzman M, Hernandez-Reyes P, et al. Microvascular damage and cardiac fibrosis detected by heart MRI are a hallmark of systemic sclerosis heart involvement. *Arthritis and Rheumatism. Conference: Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals* 2011;63(10 SUPPL. 1).
- 31 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(11):3827-36.

- 32 Jacobsen S, Halberg P, Ullman S, et al. Clinical features and serum antinuclear antibodies in 230 Danish patients with systemic sclerosis. *Br. J. Rheumatol.* 1998;37(1):39-45.
- 33 Denton C, Guillevin L, Krieg T, et al. Auto-antibody status and disease manifestations of patients with scleroderma associated digital ulcers: Data from the duo registry. *Rheumatology* 2011;50:iii136.
- 34 Ceribelli A, Cavazzana I, Franceschini F, et al. Anti-Th/To are common antinucleolar autoantibodies in Italian patients with scleroderma. *J. Rheumatol.* 2010;37(10):2071-5.
- 35 de Souza Muller C, dos Santos Paiva E, Azevedo VF, Radominski SC, Filho JHCL. Autoantibody profile and clinical correlation in a group of patients with systemic sclerosis in southern Brazil. *Revista Brasileira de Reumatologia* 2011;51(4):314-24.
- 36 Steen VD. Autoantibodies in systemic sclerosis. *Semin. Arthritis Rheum.* 2005;35(1):35-42.
- 37 Rodriguez-Reyna TS, Hinojosa-Azaola A, Martinez-Reyes C, et al. Distinctive autoantibody profile in Mexican Mestizo systemic sclerosis patients. *Autoimmunity* 2011;44(7):576-84.
- 38 Hesselstrand R, Scheja A, Shen GQ, Wiik A, Akesson A. The association of antinuclear antibodies with organ involvement and survival in systemic sclerosis. *Rheumatology* 2003;42(4):534-40.
- 39 Picillo U, Migliaresi S, Marcialis MR, Ferruzzi AM, Tirri G. Clinical setting of patients with systemic sclerosis by serum autoantibodies. *Clin. Rheumatol.* 1997;16(4):378-83.
- 40 Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. *Arthritis Rheum.* 1994;37(1):75-83.
- 41 Hanke K, Dahnrich C, Bruckner CS, et al. Diagnostic value of anti-topoisomerase I antibodies in a large monocentric cohort. *Arthritis Research and Therapy* 2009;11(1).
- 42 Aggarwal R, Lucas M, Fertig N, Oddis CV, Medsger TA, Jr. Anti-U3 RNP autoantibodies in systemic sclerosis. *Arthritis Rheum.* 2009;60(4):1112-8.