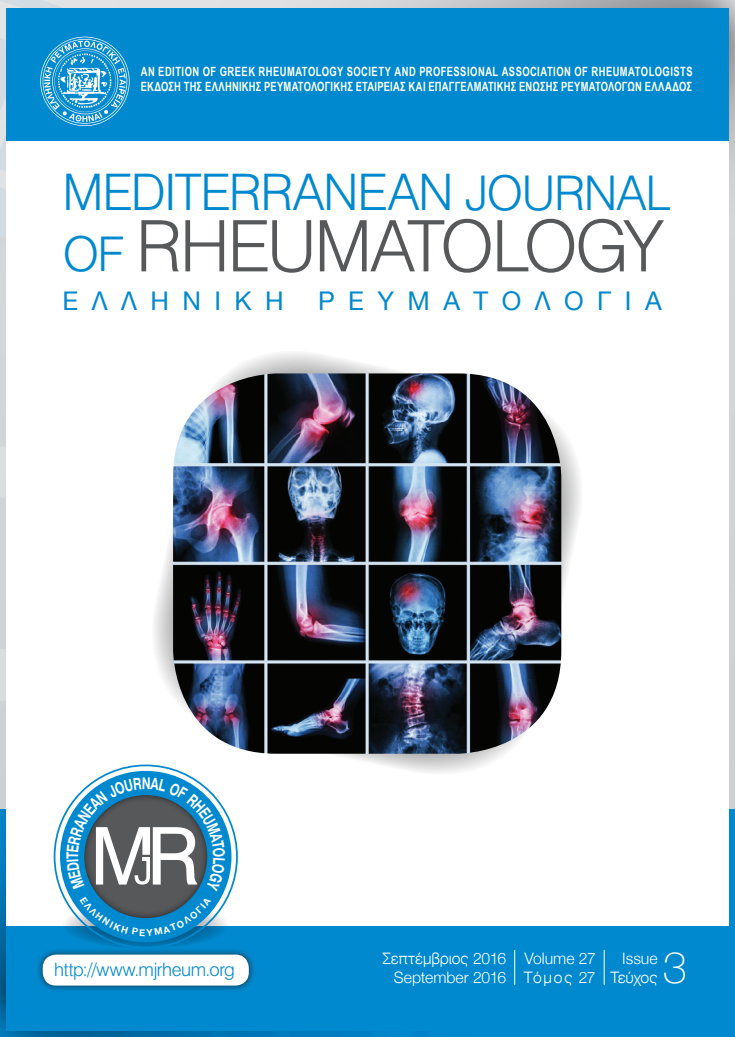
Evolution and management of late onset cardiac involvement in a contemporary systemic sclerosis cohort

Pinelopi Konstantopoulou, Elias Gialafos, Ioannis Moyssakis, Christos Tountas, Maria Konsta, George Vaiopoulos, Petros P. Sfikakis

Mediterr J Rheumatol 2016; 27(3):102-7



E-ISSN: 2459-3516

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY
ΕΛΛΗΝΙΚΗ ΡΕΥΜΑΤΟΛΟΓΙΑ
27
3
2016

ORIGINAL PAPER

Evolution and management of late onset cardiac involvement in a contemporary systemic sclerosis cohort

Pinelopi Konstantopoulou[1], Elias Gialafos[2], Ioannis Moyssakis[2], Christos Tountas[1], Maria Konsta[1], George Vaiopoulos[1], Petros P. Sfikakis[1]

[1]Rheumatology Unit, First Department of Propaedeutic and Internal Medicine, Athens University Medical School, [2]Cardiology Department, Laikon Hospital, Athens, Greece

ABSTRACT

Objective: To prospectively assess late cardiac involvement in asymptomatic patients with systemic sclerosis (SSc). **Patients and Methods:** Sixty-six selected patients (60 women, 41 with diffuse SSc), aged 50.3±12.4 years (mean±SD) with at least a 3-year disease duration (8.2±5.9) having left ventricular ejection fraction (LVEF) >55% by ultrasound were followed-up every 3-6 months for 5.5±2.1 years (range 3-10). A 12-lead electrocardiogram and 24-hour heart rate recording were performed at least annually and every 1-3 years, respectively. None were receiving bosentan or iloprost at baseline. **Results:** Baseline electrocardiographic abnormalities included incomplete (10.6%) and complete right bundle branch block (1.5%), left bundle branch block (6.0%), left anterior hemiblock (6.0%) and LV hypertrophy (1.5%). Baseline LV diastolic dysfunction and systolic pulmonary pressure >40mmHg were also found by ultrasound in 15.1% and 21.2%, respectively. During follow-up, no myocardial infarction or cardiac death occurred, but 4.5% and 2.1% of patients developed pericarditis and atrial fibrillation, respectively, and 6.1% needed pacemaker implantation. Although none of the patients developed heart failure at follow-up end, the mean LVEF decreased significantly. At follow-up end, the use of calcium channel blockers and angiotensin-converting enzyme inhibitors administration was not increased, but 16.7% and 22.7% of patients were on anti-arrhythmic drugs and bosentan, respectively. No major differences in evolution and management between diffuse and limited SSc were noted. **Conclusion:** Late cardiac involvement is common but relatively benign in a typical contemporary SSc cohort, probably due to prompt diagnosis and improved therapeutic approaches.

Corresponding author:
Pinelopi Konstantopoulou, MD, PhD
First Department of Propedeutic and Internal Medicine
Laikon Hospital, Ag. Thoma 17,
11527 Athens, Greece
Tel: +30 2107456461
Fax: +30 213 2061755
Email: nellykon2001@yahoo.com

Mediterr J Rheumatol 2016;27(3):102-7

https://doi.org/10.31138/mjr.27.3.102

Keywords: cardiac involvement, systemic sclerosis, evolution.

Cite this article as: Konstantopoulou P, Gialafos E, Moyssakis I, Tountas C, Konsta M, Vaiopoulos G, Sfikakis P P. Evolution and management of late onset cardiac involvement in a contemporary systemic sclerosis cohort. Mediterr J Rheumatol 2016;27(3):102-7.

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread vascular lesions and fibrosis of the skin and internal organs, resulting in increased morbidity and mortality. The leading cause of mortality is cardiac involvement which may occur early or late in the disease course.[1,2] Although the frequency of cardiac abnormalities has been identified in autopsy series in more than 80% of the patients, a clinical diagnosis of cardiac involvement is made much less often, especially in patients with active lung disease.[3-6] Cardiac involvement includes pericardial and myocardial disease and also disorders of cardiac rhythm and conduction.[7] Typical pathological findings include disseminated plaques of myocardial fibrosis, normal epicardial coronary arteries and arteriolar concentric intimal hypertrophy, which leads to impaired coronary reserve.[8,9] A multitude of electrocardiographic abnormalities have been described in patients with SSc, but the prevalence of such disorders varies greatly, ranging from 9 to 98 percent.[10,11] Abnormalities reported have included atrial (20-30%) and ventricular arrhythmias (7-13%),[11-14] and conduction system disease including right and left bundle branch block and heart block (2-7%).[11,13,15-17] Conduction defects and arrhythmias are thought to be a result of fibrosis or ischemia of the conduction system.[18] Left ventricular hypertrophy has been noted both with and without systemic hypertension.[13,17,19] Similarly, right ventricular hypertrophy has been reported.[11,16,17]

A recent meta-analysis of literature revealed that the standardized mortality ratio in SSc has not significantly changed over the past 40 years.[1] However, other evidence suggests that survival has been improved during the last decade.[20] The present prospective study was carried out to evaluate the incidence and evolution of late cardiac involvement and describe its management in contemporary SSc patients who survived the first 3 years after disease onset without clinically overt cardiac disease.

PATIENTS AND METHODS

Sixty-six adult patients (60 women) with SSc of at least 3 years duration (range 3–22 years) and having no clinical evidence of cardiac involvement and left ventricular ejection fraction (LVEF) higher than 55% by echocardiography, participated in this observational study which was conducted between 2002 and 2012 in our centre. At baseline, none had a history of coronary artery disease, valvular or congenital heart disease, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, renal failure, diabetes mellitus, or arterial hypertension prior to SSc diagnosis; serum concentrations of thyroid hormones were within normal limits in all patients. Moreover, none of these patients at baseline was receiving anti-arrhythmic drugs. Patients where followed up for at least 3 years from baseline (mean 5.5±2.1, range 3-10 years).

Complete clinical and laboratory evaluation, standard electrocardiography (ECG), 24-hour ambulatory ECG recordings, transthoracic echocardiography, high-resolution computed tomography (CT) of the chest and lung function tests, including measurements of forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO), as described were performed at baseline.[21] Patients were clinically followed up every 3-6 months. ECG, echocardiography and the lung function tests were performed at least annually, whereas 24-hour ECG recordings were performed at least every 1-3 years. Immediate decisions and pharmaceuticals interventions were made according to the findings.

The study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee. All participants provided informed consent.

Electrocardiography and 24-hour ambulatory electrocardiography recordings

A 12-lead digital ECG (CardioControl NV, Netherlands) was recorded in the supine resting position for 5 min. Twenty-four hour recordings started between 11.00 a.m. and 12.00 a.m. using a three-channel recorder (version 3.1 ELA Medical, France). All arrhythmias and conduction system abnormalities were recorded. Ventricular arrhythmias were categorised according to Lown and Wolf Classification,[22] as class 0 (no ventricular ectopic beat); class I (≤720 ventricular ectopic beats/24h); class II (≥720 ventricular ectopic beats/24h); class III (multiform ventricular extrasystole or bigeminal or trigeminal extrasystole); class IVA (ventricular extrasystoles in couplets); class IVB (non-sustained ventricular tachycardia); and class V (ventricular extrasystole of the R-on-T type).

Echocardiographic measurements

Standard echocardiographic examination was always performed by the same experienced operator (Hewlett-Packard, Sonos 2500, Andover, Massachusetts, USA). The left ventricular ejection fraction (LVEF) was calculated by the method of Simpson.[23,24] The early diastolic peak flow (E) and atrial peak flow (A) were recorded by the pulse wave Doppler with the sample volume at the tip of the mitral leaflet. The E/A ratio, the isovolumic relaxation time as well as the deceleration time of E wave, were calculated as indicators of LV diastolic function.[23] Pulmonary artery systolic pressure (PASP) was estimated by continuous wave Doppler recorded in the apical four-chamber or parasternal short axis view as the peak systolic pressure gradient across the tricuspid valve (peak regurgitation velocity) plus the estimated right atrial pressure.[25] PASP >40 mmHg was

defined as abnormal.[26] Detailed valvular and pericardial evaluation was assessed by two-dimensional and Doppler (color, PW, CW) images.

Statistical analysis

Continuous variables were compared using *t*-tests (or non-parametric equivalent when appropriate). Categorical variables were compared using the chi-squared statistic. Results are presented as the mean±standard deviation (SD) or percentage, or as median values (50th quartile) with interquartile ranges (25th to 75th quartiles), as appropriate. A p-value less than 0.05 was considered significant.

RESULTS

Table 1 summarizes SSc patients' characteristics at baseline and at the end of the follow-up. Fourteen patients (21.2%) had elevated PASP and 10 (15.1%) diastolic dysfunction of LV at baseline. Among the 66 patients, 7 (10.6%) and 1 (1.5%) had incomplete and complete right bundle branch block (RBBB), respectively, 4 had left bundle branch block (LBBB) (6.0%), 4 had left anterior hemiblock (LAH) (6.0%) and one (1.5%) had LV hypertrophy (**Table 2**). Ten patients had Lown class IV ventricular arrhythmias (5 patients had couplets of ventricular beats and 5 patients had non-sustained ventricular tachycardia). None presented an R-on-T phenomenon (Lown class V) (**Table 3**). Furthermore, serious ventricular arrhythmias were associated with PASP>40mmHg (p=0.016), especially in the limited type of the disease (p=0.044), with a tendency to occur in subjects with oesophageal involvement (p=0.053). Notably, more than one half of the patients with PASP>40mmHg developed serious ventricular arrhythmias (Lown>IV).

During a follow–up period of 5.5±2.1 years (range 3-10), 4 patients died from other than primary cardiac causes (pulmonary failure, respiratory infection, renal crisis and pulmonary arterial hypertension, respectively). None of the patients developed symptomatic coronary artery disease. Three patients developed pericarditis (4.5%) and 1 hypertrophic cardiomyopathy (1.5%). Additionally, 8 patients (12.1%) developed atrial fibrillation and four patients (6.0%) had a pacemaker implanted (3 and 1 for atrio-ventricular block and tachycardia-bradycardia syndrome, respectively) (**Table 4**). No significant change regarding the number of patients with elevated PASP was observed when comparing baseline and follow-up end. However, there was a significant increase in the number of patients with diffuse SSc and LV diastolic dysfunction (p=0.0127) (**Table 1**). The patients with disease duration >5 years when entering the study were more prone to develop diastolic dysfunction at the end of the study (p=0.01). Furthermore, although none of the patients developed systolic dysfunction of the LV, there was a significant reduction of LVEF (p=0.049) (**Table 1**).

Table 3 shows the evolution of the ventricular arrhythmias. At follow-up end, episodes of serious arrhythmias (Lown class>3) were not increased, although there was a significant reduction of the patients without ectopic beats (Lown class 0, p=0.016).

As shown in **Table 5**, the use of cardiological drugs was increased from baseline through follow-up end, while

Table 1. Characteristics of patients with SSc at baseline and after 5.5±2.1 years (range 3-10)*.

	All patients			Diffuse skin involvement			Limited skin involvement		
	Baseline	Follow-up end	p	Baseline	Follow-up end	p	Baseline	Follow-up end	p
n	66	66		41	41		25	25	
Men/women	6/60	6/60		4/37	4/37		2/23	2/23	
Age (years)	50.3± 12.4	55.8±12.6		49.1± 11.6	54.6± 11.8		52.4±13.6	57.9± 13.8	
Disease duration (years)	8.2±5.9	13.7±7		8.3±6.1	13.7±7.4		8.2± 5.8	13.7± 6.5	
Scl70 positive (%)	40 (60.6)	40 (60.6)		34 (82.9)	34 (82.9)		6 (24)	6 (24)	
ACA positive (%)	18 (27.3)	18 (27.3)		1 (2.4)	1 (2.4)		17 (68)	17 (68)	
PASP>40 mmHg (%)	14 (21.2)	10 (15.1)	NS	6 (14.6)	6 (14.6)	NS	8 (32)	4 (16)	NS
LVEF (%)	60.7± 5	59.3± 4.4	**0.049**	61.2±4.7	59.9±4.1	NS	59.9± 5.5	58.4±4.8	NS
Diastolic dysfunction of LV (%)	10 (15.1)	25 (37.9)	**0.0026**	7 (17.1)	17 (41.5)	**0.02**	3 (12)	8 (32)	NS

* For patients who died, data recorded at their last follow-up evaluation are presented.

Table 2. Baseline Electrocardiographic findings in patients with SSc.

	All patients (n=66)	Diffuse skin involvement (n=41)	Limited skin involvement (n=25)	p
LBBB, n (%)	4 (5.8)	2 (50)	2 (50)	0.56
RBBB, n (%)	1 (1.5)	0 (0)	1 (100)	0.33
Incomplete RBBB, n (%)	7 (10.6)	4 (57.1)	3 (42.9)	0.99
LAH, n (%)	4 (6.0)	4 (100)	0 (0)	0.24
LVH,n (%)	1 (1.5)	4 (100)	0 (0)	0.99

LBBB: Left Bundle Branch Block, RBBB: Right Bundle Branch Block, LAH: Left Anterior Hemiblock, LVH: Left ventricular Hypertrophy.

Table 3. Evolution of ventricular arrhythmias.

Lown class	Baseline n (%)	Follow-up end n (%)	p
0	11(16.6)	2 (3.2)	0.016
I	35 (53)	45 (68.2)[!]	NS
II	5 (7.6)	10 (15.85)	NS
III	5 (7.6)	1 (1.59)	NS
IVA	5 (7.6)	5 (7.9)[$]	NS
IVB	5 (7.6)	3 (4.76)	NS
V	0 (0)	0 (0)	NS

[!]3 patients are paced.
[$]1 patient is paced.

Table 4. Characteristics of late cardiac involvement in previously asymptomatic patients with SSc during 5.5 years of follow-up.

Characteristics	All patients (n=66)	Diffuse skin involvement (n=41)	Limited skin involvement (n=25)	p
Pericarditis (%)	3 (4.5)	3 (100)	0 (0)	0.5
Cardiomyopathy (%)	1 (1.5)	1 (100)	0 (0)	0.99
Atrial fibrillation (%)	8 (12.1)	5 (62.5)	3 (37.5)	0.99
Pacemaker (atrioventricular block, tachycardia-bradycardia syndrome)	4 (6.0)	2 (50)	2 (50)	0.56

Table 5. Cardiological drugs at baseline and follow-up end.

	All patients (n=66) (%)		Diffuse skin involvement (n=41) (%)		Limited skin involvement (n=25) (%)	
Drugs	**Baseline**	**Follow-up end**	**Baseline**	**Follow-up end**	**Baseline**	**Follow-up end**
Ca++ channel blockers	32 (48.5)	34 (51.5)	20 (48.8)	22 (53.7)	12 (48)	12 (48)
ACE inhibitors	14 (21.2)	16 (24.2)	10 (24.4)	13 (31.7)	4 (16)	3 (12)
AT1antagonists	3 (4.5)	4 (6.0)	2 (4.9)	2 (4.9)	1 (4)	2 (8)
Antiplatelet agents	17 (25.7)	17 (25.7)	13 (31.7)	13 (31.7)	4 (16)	4 (16)
Diuretics	4 (6.0)	6 (9.0)	2 (4.9)	3 (7.3)	2 (8)	3 (12)
Antiarrhythmics	0 (0)	11 (16.7)	0 (0)	6 (14.6)	0 (0)	5 (20)
Anticoagulants	0 (0)	3 (4.5)	0 (0)	2 (4.9)	0 (0)	1 (4)
Endothelin inhibitors	0 (0)	15 (22.7)	0 (0)	12 (29.2)	0 (0)	3 (12)

16.7% and 22.7% of the patients were using anti-arrhythmic drugs and endothelin inhibitors, respectively, at the end of the study. Finally, statistical analysis did not reveal major differences in evolution and management of late cardiac involvement between diffuse and limited SSc.

DISCUSSION

To the best of our knowledge, this is the first prospective cardiological study in asymptomatic SSc patients who survived the first 3 years of the disease. The results show that about 1 out of 5 of such patients, with mean disease duration of 8 years at baseline, will develop atrial fibrillation or need pacemaker implantation during the next 5 years, irrespective of the extent of skin involvement. In the larger cross-sectional study to date, 183 SSc patients underwent 24-hour Holter recording; ventricular ectopy occurred in 67% of patients, while episodes of ventricular tachycardia were also observed in 7% of patients. Importantly, the presence of ventricular ectopy has been strongly correlated with total mortality and with sudden cardiac death.[27] Consistent with our findings, ventricular tachycardia runs were present in 8% of SSc patients.[28] These types of arrhythmias are considered serious since they increase the risk for sustained ventricular tachycardia, ventricular fibrillation and sudden cardiac death even in apparently healthy individuals.[29-30] In the present study, an association between elevated PASP and Lown classes>3 was observed. Furthermore, at follow-up end, episodes of Lown class>3 were not increased, probably because the patients were under very close monitoring and immediate decisions were made regarding their treatment with anti-arrhythmic drugs.

Elevated PASP by echocardiography was found in 21.2 and 15.15% of patients during the first and the last recording, respectively. It should be noted that no endothelin inhibitors were administered to the patients when entering the study, while there was an extensive use of them during the follow up, mainly for the treatment of digital ulcers. This fact may explain the absence of PASP deterioration. On the other hand, none of the patients underwent right heart catheterization, which is the 'gold standard' for the diagnosis of PAH.

The use of calcium-channel blockers has been shown to exert a protective role against the development of LV dysfunction in different series.[2,31-33] Since about half of our patients were on these drugs at baseline, this may explain why none had a LVEF lower than 50% at follow-up end. Because microvascular functional and structural abnormalities rather than macrovascular coronary involvement characterize SSc,[34] calcium channel blocker administration may also explain the absence of fatal cardiovascular events in our cohort which does not comprise patients with diabetes or history of coronary artery disease.

The presence of diastolic dysfunction in patients with SSc has been extensively described.[26,35-36] However, the distinction between pathological findings and age-related changes or other confounding factors may be hard to ascertain. In the largest cross-sectional study, the authors reported the presence of diastolic abnormalities in 101 of 570 patients (17.7%). However, 48 (8.4%) patients had a restrictive mitral flow pattern, which is unequivocally abnormal, while 53 (9.3%) patients had delayed diastolic relaxation, which, in the absence of a control group, does not allow formal conclusions to be made.[26] In one controlled study, using pulsed TDE, 30 of 100 patients had definite abnormal left ventricular filling.[37] Overall, the prevalence of diastolic dysfunction was increased compared with age and gender-matched controls,[37] and ranged from 17 to 30%.[26,37] Our results are consistent with the above; the presence of diastolic dysfunction increased significantly from 15.1% of patients at baseline to 38% at the end of the follow-up. Patients with diffuse SSc and those with disease duration>5 years when entering the study were more prone to developing diastolic dysfunction. Finally, pericarditis occurred in only 4.5% of patients during follow-up. Pericardial involvement in autopsy studies has been reported in 77.5% of SSc patients.[38] Pericardial effusion has been noted in 43% of patients versus 4% of controls, but only 14% had a significant effusion, according to a controlled study.[35]

Acknowledging the relatively small sample size of this study, we conclude that late cardiac involvement is common but relatively benign in a typical contemporary SSc cohort, irrespective of the extent of skin involvement. Notably, asymptomatic patients commonly develop atrial fibrillation or need pacemaker implantation over the next years. Overall, our results suggest that optimal care, which includes at least annual screening and the use of innovative drugs in combination with the conventional cardiological drugs, may prevent fatal cardiovascular events in these patients.

ACKNOWLEDGMENTS

Dr. Christos Tountas has received an educational grant from the Hellenic Cardiological Society. Rheumatology 2012

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2012;51:1017-26.
2. Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis. Rheumatology (Oxford) 2006;45:iv14-17.
3. Weiss S, Stead E A, Warren J V, Bailley O T. Scleroderma heart disease: with a consideration of certain other visceral manifesta-

tion of scleroderma. Arch Intern Med 1943;71:749-76.
4. Anvari A, Graninger C, Schneider B, Sochor H, Weber H, Schmidinger H. Cardiac involvement in Systemic Sclerosis. Arthritis Rheum 1992;35:1356-61.
5. Murata I, Takenaka K, Yoshinoya S, Kikuchi K, Kiuchi T, Tanigawa T, et al. Clinical evaluation of pulmonary hypertension in Systemic Sclerosis and related Disorders. Chest 1997;111:36-43.
6. Medsger T A, Masi A T, Rodnan GP, Benedek T G, Robinson H. Survival with systemic sclerosis (scleroderma). A life table analysis of clinical and demographic factors in 309 patients. Ann Intern Med 1971;75:369-76.
7. Owens G, Follansbee W. Cardiopulmonary manifestations of systemic sclerosis. Chest 1987;91:118-27.
8. Follansbee W P, Curtiss E I, Medsger T A, Steen V D, Uretsky B F, Owens G R, et al. Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N Engl J Med 1984;310:142-8.
9. Kahan A, Nitenberg A, Foult J M, Amor B, Menkes C J, Devaux J Y, et al. Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985;28:637-46.
10. Windesheim J H, Parkin T W. Electrocardiograms of ninety patients with acrosclerosis and progressive diffuse sclerosis (scleroderma). Circulation 1958;17:874-81.
11. Oram S, Stokes W. The heart in scleroderma. Br Heart J 1961;23:243-59.
12. Escudero J, McDevitt E. The electrocardiogram in scleroderma: analysis of 60 cases and review of the literature. Am Heart J 1958;56:846-55.
13. Ridolfi R L, Bulkley B H, Hutchins G M. The cardiac conduction system in progressive systemic sclerosis. Clinical and pathologic features of 35 patients. Am J Med 1976;61:361-6.
14. Gaffney F A, Anderson R J, Nixon J V, Blomqvist C G. Cardiovascular function in patients with progressive systemic sclerosis (scleroderma). Clin Cardiol 1982;5:569-76.
15. James T N. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974;50:844-56.
16. Gottdiener J S, Moutsopoulos H M, Decker J L. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979;66:391-8.
17. Sackner M A, Heinz E R, Steinberg A J. The heart in scleroderma. Am J Cardiol 1966;17:542-59.
18. Steen V. The heart in systemic sclerosis. Curr Rheumatol Rep 2004;6:137-40.
19. de Groote P, Gressin V, Hachulla E, Carpentier P, Guillevin L, Kahan A, et al: ItinerAIR-Scleroderma Investigators. Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis. Ann Rheum Dis 2008;67:31-6.
20. Panopoulos ST, Bournia VK, Sfikakis PP. Is vasculopathy associated with systemic sclerosis more severe in men? J Rheumatol 2013;40:46-51.
21. Gialafos E, Konstantopoulou P, Voulgari C, Giavri I, Panopoulos S, Vaiopoulos G, et al. Abnormal spatial QRS-T angle, a marker of ventricular repolarisation, predicts serious ventricular arrhythmia in systemic sclerosis. Clinical and experimental Rheumatology 2012;30:327-31.
22. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130.
23. Sciller N B, Shah P M, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quanitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography, Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.
24. Lang R M, Bierig M, Devereux R B, Flachskampf F A, Foster E, Pellikka P A, et al. American Society of Echocardiography's Nomeclature and Standards Committee; T ask Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Asociation; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79-108.
25. Yock P G, Popp R L. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657-62.
26. Mukerjee D, St George D, Knight C, Davar J, Wells AU, Du Bois R M, et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology (Oxford) 2004;43:461-6.
27. Kostis J B, Seibold J R, Turkevich D, Masi A T, Grau R G, Medsger T A Jr., et al. Prognostic importance of cardiac arrhythmias in systemic sclerosis. Am J Med 1988;84:1007-15.
28. Morelli S, Piccirillo G, Fimognari F, Sgreccia A, Ferrante L, Morabito G, et al. Twenty-four hour heart period variability in systemic sclerosis. J Rheumatol 1996;23:643-5.
29. Morshedi-Meibodi A, Evans JC, Levy D, Larson MG, Vasan RS. Clinical correlates and prognostic significance of exercise-induced ventricular premature beats in the community: the Framingham Heart Study. Circulation 2004;109:417-22.
30. Katritsis D G, Camm A J. Nonsustained ventricular tachycardia: where do we stand? Eur Heart J 2004;25:1093-9.
31. Allanore Y, Meune C, Vonk M C, Airo P, Hachulla E, Caramaschi P, et al. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of systemic sclerosis patients. Ann Rheum Dis 2010;69:218-21. doi:10.1136/ard.2008.103382.
32. Kahan A, Devaux J Y, Amor B, Menkès C J, Weber S, Guérin F, et al. Pharmacodynamic effect of nicardipine on left ventricular function in systemic sclerosis. J Rheumatol 2004;31:1941-5.
33. Meune C, Allanore Y, Devaux J Y, Dessault O, Duboc D, Weber S, et al. High prevalence of right ventricular systolic dysfunction in early systemic sclerosis. J Rheumatol 2004;31:1941-5.
34. Dimitroulas T, Giannakoulas G, Karvounis H, Garyfallos A, Settas L, Kitas G D. Micro- and Macrovascular Treatment Targets in Scleroderma Heart Disease. Curr Pharm Des 2014;20:536-44.
35. Handa R, Gupta K, Malhotra A, Jain P, Kamath P K, Aggarwal P, et al. Cardiac involvement in limited systemic sclerosis: non-invasive assessment in asymptomatic patients. Clin Rheumatol 1999;18:136-9.
36. Maione S, Cuomo G, Giunta A, Tanturri de Horatio L, La Montagna G, Manguso F, et al. Echocardiographic alterations in systemic sclerosis: a longitudinal study. Semin Arthritis Rheum 2005;34:721-7.
37. Meune C, Avouac J, Wahbi K, Cabanes L, Wipff J, Mouthon L, 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;58:1803-9.
38. Byers R J, Marshall D A, Freemont A J. Pericardial involvement in systemic sclerosis. Ann Rheum Dis 1997; 56:393-4.