

Preliminary Study of Cardiovascular Manifestations and Cardiac Severity Scale in 58 Patients with Systemic Sclerosis in Iran Using the Medsger Scale

Hadi Poormoghim, MD^{1*}, Mohamad Ali Poorkarim, MD¹, Maziar Moradi Lakeh, MD², Behnaz Nozary Heshmati, MD¹, Simin Almasi, MD¹, Mojtaba Hakim, MD³

¹Firouzgar Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran.

²Department of Community Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran.

³Labafi-Nejad Hospital, Shaheed Beheshtee University of Medical Sciences, Tehran, Iran.

Received 28 July 2009; Accepted 10 November 2009

Abstract

Background: Cardiac involvement in systemic sclerosis (SSc) is more prevalent than previously thought. In this study, the frequency and severity of cardiovascular involvement were assessed in SSc patients referred to Firouzgar Hospital.

Methods: Fifty-eight patients with SSc, selected from the data bank of SSc patients, were reviewed for the frequency and severity of 8 organ involvements in this case series.

The preliminary severity scale, published by international SSc study groups, was employed for the determination of the severity grade in the cardiovascular system. In the cardiac scoring scale, grade 0 represents normal heart (no cardiac involvement), grade 1 denotes mild involvement [electrocardiography (ECG) conduction defect and a left ventricular ejection fraction (LVEF) of 45-49%], grade 2 signifies moderate involvement (arrhythmia, LVEF = 40-44%), grade 3 indicates severe involvement (LVEF <40%), and grade 4 stands for end stage (congestive heart failure and arrhythmia requiring treatment).

Results: In this study, 24 (41.4%) patients were in the diffuse cutaneous (dcSSc) subset. The female to male ratio was 10.5:1, and the mean duration from symptom onset to diagnosis was 7.35 years for the dcSSc subset and 8.41 years for the limited cutaneous (lcSSc) subset of disease, there being no significant difference. Cardiac involvement in this series was seen in 13 (22.4%) cases; and there was no significant difference in terms of frequency and severity between the two disease subgroups (p value = 0.96 and p value = 0.46 respectively).

Conclusion: Our findings showed that the cardiac involvement in this series was infrequent and that there was no significant difference in the severity of cardiovascular involvement between the two subtypes of SSc in the late stage of the disease.

J Teh Univ Heart Ctr 1 (2010) 14-18

Keywords: Scleroderma, systemic • Connective tissue diseases • Heart

Introduction

Systemic sclerosis (SSc) is a connective tissue disorder

characterized by vascular lesion and widespread fibrosis in organs such as skin, gut, lung, heart, and kidneys. Clinically, there is a broad spectrum of symptoms from widespread

*Corresponding Author: Hadi Poormoghim, Associate Professor of Rheumatology, Iran University of Medical Sciences and Health Care Services, Firouzgar Teaching Hospital, Valye-aser Avenue, Tehran, Iran. 1593748711. Tel: +98 21 88052252. Fax: +98 21 88052967. Email: hpoormoghim@iums.ac.ir



severe skin thickening (diffuse) to skin thickening limited to distal extremities and/or face (limited). In the diffuse form, skin involvement is limited to hands, body, and face; whereas in the limited form, skin involvement is limited to hands and extremities lower than elbows and knees.

Cardiac involvement in SSc seems to be more prevalent than previously thought,¹ as shown by improved invasive and non-invasive diagnostic techniques for detecting heart disease.²⁻⁵ Cardiopulmonary, renal, and extensive skin involvement is poor prognosis and the leading cause of early death in SSc.⁶

To determine the abundance of cardiac involvement, the present study drew upon such different modalities as autopsy, exercise test, radioisotope scan, chest X-ray, ECG, and echocardiography.⁶⁻⁸ The severity of cardiac disease is usually determined using the two scoring methods of Clement and Medsger. The former is currently less favored in clinical trials, but the latter is regarded as more practical and is accepted by international SSc study groups.

The present study was designed to address the dearth of data on the severity and frequency of cardiac involvement in SSc patients in Iran.

Patients and methods

The SSc data bank in Firouzgar Hospital Rheumatology Department contains information on 67 patients (Until January 2007). Patients fulfilling the preliminary criteria of the American Rheumatism Association were recruited into this study, and 4 patients diagnosed as having SSc overlap with other connective tissue disease in addition to 5 patients whose cardiac involvement was secondary to pulmonary involvement were excluded. In total, 58 patients were included in the study.

During a 6-month period after the first visit to our clinic, core set variables of all the patients in this case series were assessed to define each organ system involvement. For cardiac involvement, traditional criteria hinging on the presence of 1 or more dichotomous variables, i.e. presence or absence of cardiomegaly, pericardial effusion, ventricular arrhythmias, conduction disturbances, axis deviations, and pathological Q waves (myocardial necrosis), were employed.^{2, 6} For cardiac severity, the preliminary severity scale, published by international SSc study groups, was utilized and the patients' files were reviewed retrospectively.⁸⁻¹⁰ The preliminary scale introduced by Medsger proposes a 9-organ disease severity scale for SSc, with "severity" defined as the total effect of the disease on the organ function. The scale has both irreversible (damage) and reversible components (activity), and the severity grading for each organ system ranges from 0 (no document) to 4 (end-stage disease).

In the cardiac scoring scale, grade 0 represents normal heart (no cardiac involvement), grade 1 denotes mild involvement [electrocardiography (ECG) conduction defect

and a left ventricular ejection fraction (LVEF) of 45-49%], grade 2 signifies moderate involvement (arrhythmia, LVEF = 40-44%),^{8, 9} grade 3 indicates severe involvement (LVEF <40%), and grade 4 stands for end stage (congestive heart failure and arrhythmia requiring treatment).

For the cardiac severity scale, each variable was primarily attributed to SSc rather than to another disorder. For example, if patients with mild (grade 1) cardiac involvement developed superimposed bacterial pneumonia with transient severe dyspnea and fibrillation (grade 2, moderate) due to hypoxia, the cardiac score was evaluated after pneumonia had resolved.

The relationship between cardiac involvement severity (cardiac scoring) and disease stage was assessed by analyzing the time periods in two disease subsets: early and late stages of the disease. Early stage was defined as diffuse cutaneous (dcSSc) < 3 years and limited cutaneous (lcSSc) < 5 years.

The analyses were performed using SPSS software version 9 released for microcomputers. The chi-square test was used for the detection of any correlation between cardiac severity and the two subsets of scleroderma, and the Fisher exact test was employed for the comparison of cardiac severity in the early and late stages of the 2 disease subsets. The Kendall Tau correlation coefficient was used to assess the correlation between cardiac severity and severity of other organ involvement.

Results

Table 1 depicts the general characteristics of the patients. There were 58 patients with a mean age \pm SD of 40.9 \pm 13.7 years and a female to male ratio of 53/5, of whom 24 (41.4%) patients were in the dcSSc subset. The mean total skin score in all the patients was 16.6, based on the modified Rodnan scoring system, and the mean duration from symptom onset to study entry was 7.3 \pm 8.5 years for the dcSSc and 8.4 \pm 8.2 years for the lcSSc subsets; there was no statistically significant difference (p value = 0.638).

Table 1. Comparisons of clinical characteristics in two subsets of patients

	lcSSc subset	dcSSc subset	total
Number of patients (%)	34 (59.6)	34 (41.4)	58 (100)
Age (y) (mean \pm SD)	41.3 \pm 14	40.3 \pm 13.4	40.8 \pm 13.7
Female/male	31/3	22/2	53/5
Mean total skin score*	12.4	22.2	16.6
Mean duration (y)**	8.41	7.35	7.97

*p value < 0.0001

**Form the onset to the first visit

lcSSc subset, Limited cutaneous subset; dcSSc subset, Diffuse cutaneous subset

Table 2 illustrates the characteristics of cardiac involvement in the patients. Cardiac involvement was detected in 13 (22.4%) and conductive disturbance in 6 (10.3%) out of the

58 SSc study patients. Axis deviation was found in 6 (10.3%) patients, all with left axis deviation. Additionally, abnormal Q waves and arrhythmia were found in 1 (1.7) and 2 (3.5) patients, respectively.

Cardiomegaly on chest x-ray, echocardiography, or ECG was found in 10 (17.2%) patients: 4 in the limited and 6 in the diffuse disease subtypes. Echocardiography revealed pericardial effusion in 9 (15.5%) patients, with a moderate-to-severe degree of pericardial effusion in 3 (5.1%) persons. As Table-3 demonstrates, there was no difference in terms of cardiac involvement between the 2 forms of scleroderma.

Table 2. Cardiac characteristics of the patients

Variable	lcSSc subset	dcSSc subset	total
Axis deviation			
Normal axis	29 (85.3)	22 (95.7)	51 (87.9)
LAD	5 (14.7)	1 (4.3)	6 (10.3)
RAD	0	0	0
Arrhythmia	1(2.9)	1 (4.3)	2 (3.5)
Abnormal Q-wave	0	1 (4.3)	1 (1.7)
Conduction defect			
None	29 (85.3)	21 (91.3)	50 (86.2)
LBBB	1 (2.9)	1 (4.3)	2 (3.4)
LAHB	3 (8.8)	0	3 (5.2)
RBBB + LAHB	1 (2.9)	0	1 (1.7)
Complete hemi block	0	1 (4.3)	1 (1.7)
Cardiomegaly	4 (11.8)	6 (25)	10 (17.2)
Pericardial effusion			
None	29 (85.3)	20 (83.3)	49 (84.5)
Mild	4 (11.8)	2 (8.3)	6 (10.3)
Moderate	0	2 (8.3)	2 (3.4)
Severe	1 (2.9)	0	1 (1.7)

*Numbers in the parenthesis are the related percentages
lcSSc subset, Limited cutaneous subset; dcSSc subset, Diffuse cutaneous subset; LAD, Left axis deviation; RAD, Right axis deviation; LBBB, Left bundle branch block; LAHB, Left anterior hemiblock; RBBB, Right bundle branch block

Table 3. Severity grade and stage of the disease in two subsets of systemic sclerosis (SSc)

Stage	Severity	Diffuse SSc	Limited SSc
Early*	Normal	5	17
	Mild	2	2
	Moderate	0	0
	Severe	1	0
Late**	Normal	13	10
	Mild	3	5
	Moderate	0	0
	Severe	0	0

*< 3 years in diffuse cutaneous subset and < 5 years in limited cutaneous subset

**> 3 years in diffuse cutaneous subset and > 10 years in limited cutaneous subset

With respect to the cardiac severity scoring of the patients, 45 (77.6%) patients scored zero (normal heart); cardiac

involvement in 13 of the 58 (22.4%) patients was detected. Seven and 5 patients in the limited and diffuse disease subsets, respectively, had mild cardiac involvement (grade 1); moderate to severe cardiac involvement was not observed in either of the two subsets; and only 1 patient with diffuse skin involvement had end-stage cardiac involvement. A comparison of the limited and diffuse subsets of patients with no cardiac involvement as group 1 and the others with mild-to-severe involvement as group 2 yielded no statistically significant difference (p value = 0.96)

In regard to the relationship between the severity of cardiac involvement and that of other systems, cardiac severity showed no correlation with the severity of dermal, peripheral vascular, renal, tendinous, muscular, and gastrointestinal systems. There was, however, a significant correlation between cardiac severity and pulmonary severity (Kendall Tau = 0.27, p value = 0.04). The relationship between cardiac severity (cardiac scoring) and disease stage in the two disease subsets was evaluated, and the time scales were analyzed in the two disease subsets in terms of early and late stages; early stage was defined as dcSSc < 3 years and lcSSc < 5 years. There were 8 (23.5) patients with the dcSSc subtype in the early disease stage < 3 years (Table 3). There was no difference in the severity grade of the two disease subtypes between the early and late stages (in early stage: p value = 0.136 and $\alpha^2 = 3.564$; in late stage: p value = 0.433 and $\alpha^2 = 0.332$).

Discussion

The female to male ratio in the present study population at a mean age±SD of 40.9±13.7 years was 53/5, which does not chime in with the results of previous epidemiological studies of SSc reporting that the disease is 3-4 times more common in women. Nonetheless, the onset of SSc in this study is in the fourth and fifth decades of life as is the case in other similar studies.^{11, 12} The mean disease duration from onset to entry in the lcSSc and dcSSc subtypes was 8.4 and 7.3 years, respectively. This means that the patients referred for treatment in the late disease stages, contributing to sample collection bias in the present study.

From a total of 58 SSc patients, 13 (22.4%) persons were found to have cardiac involvement and most of these patients (12/13 [92%]) showed mild severity of involvement.

In the Janosik et al.¹³ study, pathological involvement of the pericardium was observed in 70%-80% of the patients at autopsy, while clinical manifestation was present in 7%-20% of the study subjects. They reported an association between pericardial effusion and cardiac involvement; pericardial effusions were small or large and had developed rapidly in some cases due to renal failure.

Echocardiography revealed pericardial effusion in 9 (15.5%) patients, moderate-to-severe pericardial effusion in 3 (5.1%) patients, and no renal failure in our study population.



It is deserving of note that echocardiography tends to be abnormal in 50% of patients and includes evidence of pericardial thickening or fluid, while clinical presentations of pericarditis and of tamponade are infrequent.¹⁶ In this series, we found axis deviation in 6 (10.3%) patients, all with left axis deviation. Arrhythmia and abnormal Q waves were present in 2 and 1 patient in each disease subset.

In the Kostis J.B. et al.¹⁴ study, electrocardiography abnormalities, including arterial and ventricular arrhythmias and conduction disturbances by ambulatory electrocardiography study, confirmed a high prevalence of both supraventricular and ventricular tachyarrhythmia. In our study, cardiomegaly on chest x-ray, echocardiography, or ECG were found in 10 (17.2%) patients: 4 in the limited and 6 in the diffuse disease subtypes. In the Clements P. J. et al.¹⁵ study of 90 patients, 44 (49%) patients were found with cardiac involvement, which was comprised of arrhythmia in 4 (4.4%), cardiomegaly in 16 (17.8%), conduction defect in 9 (10%), pericardial effusion in 9 (10%), axis deviation in 18 (20%), and pathological Q wave in 12 (13.3%). The SD of the duration of SSc prior to entry was 6.6 ± 7.8 years, and 39 patients entered the study within 3 years of disease onset. In a study of cardiac involvement by Geirsson A. J. et al.,¹⁶ 40 patients with SSc and disease duration of 6 years were included in study. Cardiomegaly and arrhythmia at rest were 57% and 7.5% in the diffuse and CREST syndrome, respectively.

There were 9 (15.5%) patients with mild-to-severe pericardial effusion in our study as opposed to the 17.6% figure in the Pittsburgh study;⁸ the incidences of pericarditis were, however, similar. In the MC Whorter et al.¹⁷ study, the incidence of pericardial effusion was 50% and that of tamponade was not high as well.

Coronary involvement was evaluated via non-invasive procedures in the present study, and no serological correlation with specific auto-antibodies was done, which can be deemed a limitation of our study.

Forty-five (77.6%) of our study population scored zero for cardiac involvement (normal heart). As was mentioned above, evidence for cardiac involvement was relatively infrequent; a comparison between the limited and diffuse subsets of patients with no cardiac involvement as group 1 and the others with mild-to-severe involvement as group 2 yielded no difference in terms of frequency between the two groups (P value = 0.46).

An assessment of the relationship between the severity of cardiac involvement (cardiac scoring) and lung involvement showed no correlation with the severity of skin involvement. Visceral involvement in the diffuse subset patients was high in the early disease stage and skin stiffness was low in the late stage. Visceral involvement gradually decreased but did not cure spontaneously. In the existing literature, the incidence of visceral involvement in the limited form is similar to that of the diffuse form except for renal and dermal involvement,

which is gradual.¹⁸⁻²⁰ By contrast, 66.7% of the patients in the diffuse subset in the present study were in the late disease stage, denoting the lack of a relationship between skin involvement and severity of lung and cardiac disease. On the other hand, skin severity is not a good indicator of the severity of visceral organ involvement, especially in the late stage. This is concordant with the results of the Ferri C et al.²¹ study.

We found no difference in the severity of cardiac involvement between the two disease subsets in the early and late stages. This result may be in consequence of either the low incidence of cardiac involvement, rendering the number of cases in each disease stage insufficient to divulge any difference, or collection bias as the patients were recruited into the study long after the disease onset.

In the Furst et al.²² study, patients with progressive SSc were matched for sex, age, and disease duration and the results showed a relationship between muscle involvement and severity of skin disease.

A point of significance is that the present study represents only a small group of SSc patients in Iran. Furthermore, the fact that the majority (55%) of our patients were in the late disease stage precludes any generalization of the results.

Conclusion

The present study represents a baseline estimate of the occurrence and severity of cardiac involvement in a small group of Iranian SSc patients. In this case series of 58 patients, a low incidence of cardiac involvement was detected. Our study also demonstrates the relative ease and applicability of severity scale measures for an assessment of cardiac involvement in SSc sufferers. The existing literature bears testament to the importance of such instruments in clinical trials.

Future studies are required to shed further light on the correlation between cardiac involvement and severity and specific auto-antibodies in scleroderma.

Acknowledgment

This study was supported by Iran University of Medical Sciences. Many thanks are due to the Deputy of Research and Technology of that university.

References

1. Roberts NK, Cabeen WR Jr, Moss J, Clements PJ, Furst DE. The prevalence of conduction defects and cardiac arrhythmias in progressive systemic sclerosis. *Ann Intern Med* 1981;94:38-40.
2. Medsger TA Jr, Masi AT, Rodnan GP, Benedek TG, Robinson H. Survival with systemic sclerosis (scleroderma): a life-table analysis

- of clinical and demographic factors in 309 patients. *Ann Intern Med* 1971;75:369-376.
3. Bennett R, Bluestone R, Holt PJL, Bywaters EGL. Survival in scleroderma. *Ann Rheum Dis* 1971;30:581-588.
 4. Sackner MA, Heine ER, Steinberg AS. The heart in scleroderma. *Am J Cardiol* 1996;17:542-559.
 5. Clements PJ, Clements P, Lachenbruch P, Paulus HE. Early undifferentiated connective tissue disease: III outcome and prognostic indicators in early scleroderma (systemic sclerosis). *Ann of Intern Med* 1993;118:602-609.
 6. Clements PJ, Furst DE, Cabeen W, Tashkin D, Paulus HE, Roberts N. The relationship of arrhythmia and conduction disturbances to other manifestation of cardiopulmonary disease in progressive systemic sclerosis (PSS). *Am J Med* 1981;71:38-46.
 7. Byers RJ, Marshall DAS, Freemont AJ. Pericardial involvement in systemic sclerosis. *Ann Rheum Dis* 1997;56:393-394.
 8. Medsger TA Jr, Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, Harris CA, Jablonska S, Jayson MI, Jimenez SA, Krieg T, Leroy EC, Maddison PJ, Russell ML, Schachter RK, Wollheim FA, Zachariae H. A disease severity scale for systemic sclerosis: development and testing. *J Rheumatol* 1999;26:2159-2167.
 9. Medsger TA Jr. Assessment of damage and activity in systemic sclerosis. *Curr Opin Rheumatol* 2000;12:545-548.
 10. Geirsson AJ, Wollheim FA, Akesson A. Disease severity of 100 patients with systemic sclerosis over a period of 14 years: using a modified Medsger scale. *Ann Rheum Dis* 2001;60:1117-1122.
 11. Medsger TA Jr, Masi AT. Epidemiology of systemic sclerosis (scleroderma). *Ann Intern Med* 1971;74:714-721.
 12. Medsger TA. Epidemiology of progressive systemic sclerosis. In: Black CM, Myers AR, eds. *Systemic Sclerosis (Scleroderma)*. New York: Gower Medical Publishing; 1985. p. 53-60.
 13. Janosik DL, Osborn TG, Moore TL, Shah DG, Kenney RG, Zuckner J. Heart disease in systemic sclerosis. *Semin Arthritis Rheum* 1989;19:191-200.
 14. Kostis JB, Seibold JR, Turkevich D, Masi AT, Grau RG, Medsger TA Jr, Steen VD, Clements PJ, Szydlo L, D'Angelo WA. Prognostic importance of cardiac arrhythmias in systemic sclerosis. *Am J Med* 1988;84:1007-1015.
 15. Clements PJ, Lachenbruch PA, Furst DE, Paulus HE, Sterz MG. Cardiac score. A semiquantitative measure of cardiac involvement that improves prediction of prognosis in systemic sclerosis. *Arthritis Rheum* 1991;34:1371-1380.
 16. Geirsson AJ, Blom-Bülow B, Pahlm O, Akesson A. Cardiac involvement in systemic sclerosis. *Semin Arthritis Rheum* 1989;19:110-116.
 17. McWhorter JE 4th, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). *Am J Med* 1974;57:566-572.
 18. Steen VD, Medsger TA Jr, Rodnan GP. D-penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. *Ann Intern Med* 1982;97:652-658.
 19. Clements PJ, Lachenbruch PA, Ng SC, Simmons M, Sterz M, Furst DE. Skin score. A semiquantitative measure of cutaneous involvement that improves prediction of prognosis in systemic sclerosis. *Arthritis Rheum* 1990;33:1256-1263.
 20. Steen VD, Medsger TA Jr, Osial TA Jr, Ziegler GL, Shapiro AP, Rodnan GP. Factors predicting development of renal involvement in progressive systemic sclerosis. *Am J Med* 1984;76:779-786.
 21. Ferri C, Bernini L, Bongiorno MG, Levorato D, Viegi G, Bravi P, Contini C, Pasero G, Bombardieri S. Noninvasive evaluation of cardiac dysrhythmias, and their relationship with multisystemic symptoms, in progressive systemic sclerosis patients. *Arthritis Rheum* 1985;28:1259-1266.
 22. Furst DE, Clements PJ, Saab M, Sterz MG, Paulus HE. Clinical and serological comparison of 17 chronic progressive systemic sclerosis (PSS) and 17 CREST syndrome patients matched for sex, age, and disease duration. *Ann Rheum Dis* 1984;43:794-801.