Left ventricular wall thickness and disease duration in systemic sclerosis

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Summary: Myocardial thickness, left ventricular functions, and right heart overloading were investigated in 80 patients with systemic sclerosis by echocardiography. Based on the left ventricular wall thickness, three groups were formed. Fifteen patients with asymmetrical left ventricular wall hypertrophy (Group 1) showed shorter mean disease duration with marked diastolic and mild systolic left ventricular functional impairment. The 25 patients with wall thinning (Group 3) had a slight increase in left ventricular diameters, impaired systolic functions and longer disease duration. Group 2 with normal wall thickness exhibited mixed changes. Patients with increased wall thickness tended to have a shorter disease duration than patients with wall thinning. Patients with systemic sclerosis showed systolic and diastolic function impairment as compared to the 18 control healthy individuals. Pericardial disease was found in 23 cases (28.7%).

Introduction

Systemic sclerosis (SSc) is a generalized autoimmune disorder characterized by fibrotic, degenerative and inflammatory changes involving the skin and certain internal organs.^{1,2} Although the cause of SSc is unknown, microvascular injury, obliterative vasculopathy, autoimmune phenomena, and increased activity of fibroblasts resulting in fibrosis are well known to occur in this disease.

Involvement of the heart is often observed in SSc, and the presence of certain cardiac symptoms influences survival.^{3,4} A wide variety of cardiac involvement can be present in SSc including pericardial disease,^{3,5–7} fibrosis of the myocardium,^{5,7–9} disturbances of the conduction system,¹⁰ impaired left ventricular systolic and/or diastolic function,^{8,11–17} asymmetrical or concentric hypertrophy of the myocardium^{8,17} and the consequences of primary or secondary pulmonary hypertension.^{18–21} Myocardial ischaemia due to microvascular injury²² and increased fibroblast and probably mast cell²³ activity are the most important pathogenic factors leading to thickening or thinning of the myocardium. The effect of cold exposure and drugs on the myocardial perfusion using thallium-201 perfusion test has also been widely tested in SSc.^{12–14,24–26}

Only a few detailed echocardiographic studies have been published on left or right ventricular function in SSc.^{7,11,17,27} In some of these previous studies, the number of patients included into the study was small.^{11,27} Detailed investigations including Doppler echocardiography have not to our knowledge been performed yet in SSc.

Patients and methods

Our data are based on the investigation of 81 patients and 18 age- and sex-matched control healthy individuals. One patient had chronic azotaemia caused by the disease and was excluded from further studies. The female/male ratio of patients was 72/8. The mean age of the patients was 50.1 ± 12.5 years (from 20 to 79). At the time of investigation, all patients fulfilled the diagnostic criteria for SSc.²⁸ Twenty-three patients belonged to the subset of diffuse cutaneous systemic sclerosis and the number of cases with limited cutaneous systemic sclerosis was 57.¹ The mean disease duration was 9 ± 8 years. The clinical and laboratory data of patients were evaluated according to a standard protocol as previously described.² The time of onset of disease was taken as the appearance of the first symptom characteristic of SSc. Beside the evaluation of the case history and the physical examination, chest roentgenogram, barium oesophageal passage, assessment of the lacrimal (Schirmer's test, break up time) and salivary

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excretion were performed in all cases. The 20 patients showing both decreased lacrimal and salivary secretion were categorized as having sicca syndrome (Table I). Lung involvement was evaluated by the presence of fibrosis on chest X-ray and spirometry. The mean blood pressures of the patients and the controls were 130/82 and 124/80 mmHg, respectively. Three patients showed mild hypertension during the period of our study. No patients with diabetes mellitus, azotaemia or clinical signs of hypothyroidism were included into this study. Seven patients and two controls were smokers. No significant differences were detected between the weight of the patients and controls. The mean of the vital capacity of patients and controls were $74.9 \pm 15\%$ and $87.1 \pm 9.5\%$ of the age, gender and body surface matched controls, respectively. Three controls showed a vital capacity less than 80%.

Sixty-nine sera (86%) was antinuclear antibody positive on HEp-2 cells by indirect immunofluorescence method. Anticentromere antibody was detected in eight and staining compatible with the presence of anti-topoisomerase I antibody in 28 sera (Table I).

Short-acting nifedipine or verapamil was taken in 58 and 11 cases, respectively. D-penicillamine in 16, pentoxifyllin in 55, vitamin E in 71, captopril in 10, colchicine in six, and H₂-receptor antagonists were administered in 20 patients, respectively. All drug administration was stopped 16 hours before the examination.

Hitachi EUB 151 equipment (Japan) with 3.5 MHz and Pedoff transducers was used for the evaluation of 164 echocardiographic parameters of patients and controls. M mode, 2D and Doppler echocardiography were performed. The following parameters were evaluated: heart rate, left ventri-

cular end-systolic diameter (ESD), end-diastolic diameter (EDD), interventricular septal systolic and diastolic thickness (IVS-ST, IVS-DT), posterior wall systolic and diastolic thickness (PWST, PWDT) and the septal and posterior wall end-systolic thickening rate (PWESTH, IVSTH). We also measured the aortic root distance (AOD), aortic valves opening distance (AVD), left atrial diameter (LAD), ratio of AOD/LAD, right ventricular diameter (RVD), and pulmonary root distance (PRD). These parameters were measured from M-mode, derived from two-dimensional long-axis view. The end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), cardiac output (CO) and the fractional shortening (FS) were also evaluated by a built-in automatic programme²⁹ using planimetry.

Regurgitation was evaluated by continuous wave Doppler. The mitral, tricuspid, aortic and pulmonary Doppler curves served for the calculation of the mean velocity (Vm), the mean pressure gradient (VmPp), peak velocity (Vp), peak velocity gradient (VpPP), ejection time (ET), peak time (PT), area of valve (VA), duration of aortic (AOET), pulmonary (PUET) ejection, and pressure half time (PHT). The time necessary to reach the Doppler curve maximal velocity (peak time: PT) and the mitral and tricuspid Doppler duration time (MIET, TRET) were also calculated. From the mitral Doppler curve the velocities of E and A waves and their ratio (E/A) were also measured. The isovolumetric relaxation time (IVRT) was calculated from the simultaneously registered continuous wave of mitral and aortic Doppler curves. The acceleration time (PT) and deceleration time (DT) of the E wave, the PT/DT, and the ratio of PT to the mitral Doppler duration (PT/MIET) were also measured. The ratio of the mitral Doppler

Table I Clinical profile of the 80 patients with systemic sclerosis

	<i>All cases</i>	<i>Group 1</i>	<i>Group 2</i>	<i>Group 3</i>
Number of cases	80	15	40	25
Diffuse cutaneous involvement	23 (29%)	7	10	6
Lung involvement	59 (74%)	13	29	17
Oesophageal dysfunction	36 (45%)	8	17	11
Sjögren's syndrome	20 (25%)	2	9	9
Subcutaneous calcinosis	6 (7%)	2	3	1
Hand contractures	23 (29%)	4	11	8
Skin pigmentary changes	40 (50%)	10	20	10
Telangiectasia	42 (52%)	9	18	15
Antinuclear antibody (HEp-2)	69 (86%)	13	34	22
Anticentromere antibody	8 (10%)	1	4	3
Staining compatible with anti-Scl 70	28 (35%)	4	16	8

Groups were formed by the end-diastolic diameter. Group 1: septal and/or posterior wall thickness ≥ 13 mm. Group 2: diastolic wall thickness is between 8–13 mm. Group 3: septal and/or posterior wall end diastolic diameter ≤ 8 mm.

duration to deceleration time of E wave was also calculated (MIET/DT). The calculation of MIVP $\times$ MVA was used for the evaluation of the peak early filling rate (PFR), where MIVP is the mitral peak velocity of the mitral Doppler, and the MVA is the mitral valvular area.³⁰ The PFR/SV ratio was also calculated. These parameters were used to evaluate the left ventricular diastolic functions.

The same investigator performed all the echocardiographic measurements. Data were encoded and blindly evaluated.

Statistical investigations

A two-tailed *t*-test was used for the comparison of the parameters between patients and controls. The same procedure was performed when the findings between SSc subgroups were compared. Linear regression analysis was also applied to correlate certain parameters.

Results

No significant differences were detected in the left ventricular diameters between the patient group and controls (ESD, EDD). Seven patients showed an end diastolic diameter (EDD) greater than 55 mm (8.7%), while the end systolic distance was above 45 mm in only three cases (3.7%). An enlarged left atrium (≥ 40 mm) was found in seven cases (8.7%).

An increased diameter in the right ventricle (≥ 23 mm by M mode) was shown in 17 cases (21.2%). Five of these cases and another 18 cases (28.7%) exhibited an enlarged (≥ 25 mm) pulmon-

ary artery diameter. A total of 36 of the patients showed increased right ventricular and/or pulmonary artery diameter compared with three of the controls (two of these controls were smokers with decreased vital capacity). From these patients, four cases of pulmonary regurgitation and another of tricuspid regurgitation were found.

Fifteen patients (18.8%) showed asymmetrical left ventricular hypertrophy (≥ 13 mm) including either the septum, or the posterior wall, or both. In cases with hypertrophy of both regions, the thickness of these two wall segments were found to be different. Thinning of the left ventricular wall (≤ 8 mm) was demonstrated in 25 cases (31.2%).

Based on the end diastolic wall thickness, patients were divided into three separate subgroups, that is, increased (Group 1), normal (Group 2) and decreased (Group 3) wall diameters. The mean ages of these groups were comparable, while a shorter mean disease duration was found in the group with wall hypertrophy as compared to the group showing thinning of left ventricular wall (Table II). A significant ($P < 0.03$) positive correlation between both the posterior and septum systolic wall thickness and the age at the onset of disease was demonstrated. The same correlation by linear regression analysis was found when the cardiac output and the stroke volume were correlated with the onset of disease ($P < 0.02$). The disease duration and the stroke volume showed a negative correlation ($P < 0.03$; data not shown).

The three groups exhibited differences in their systolic and diastolic functions. The end systolic thickening in Group 1 was found to be significantly decreased as compared to Group 3 (data not shown).

With regard to the parameters characteristic of

Table II Systolic functions of patients with different wall thickness in systemic sclerosis

	All cases	Controls	Group 1	Group 2	Group 3
Number of cases	80	18	15	40	25
MDD (years)	9.0 $\pm$ 8	—	5.6 $\pm$ 4.7**	8.9 $\pm$ 8.1	11.6 $\pm$ 8.8**
MA (years)	50.1 $\pm$ 12.5	48.8 $\pm$ 6.2	51.5 $\pm$ 12.4	49.1 $\pm$ 11.4	50.1 $\pm$ 9.5
AO (years)	40.8 $\pm$ 11.5	—	45.9 $\pm$ 13*	40 $\pm$ 11.9	38.6 $\pm$ 8.9*
EDV (cm ³)	103 $\pm$ 28.5	106.4 $\pm$ 19.1	121.8 $\pm$ 31.1***	104.5 $\pm$ 29	88.5 $\pm$ 17.3***
ESV (cm ³)	56.5 $\pm$ 20.7	54.3 $\pm$ 18.8	67.5 $\pm$ 22.6**	57.3 $\pm$ 21.1	48.7 $\pm$ 15.8**
SV (cm ³)	46 $\pm$ 13.5**	53.6 $\pm$ 8.1**	54.8 $\pm$ 13.9***	47.1 $\pm$ 13.3	39.7 $\pm$ 10.7***
CO (l/min)	3.8 $\pm$ 1.2	3.8 $\pm$ 0.8	4.3 $\pm$ 0.9**	3.86 $\pm$ 1.4	3.3 $\pm$ 1**
EF (%)	45.2 $\pm$ 9.5**	51.7 $\pm$ 9.2**	44.8 $\pm$ 8.1	45.4 $\pm$ 9.2	45.3 $\pm$ 11.1
FS (%)	19.7 $\pm$ 6.2*	23.7 $\pm$ 6*	19.7 $\pm$ 5.1	19.3 $\pm$ 6.3	20.2 $\pm$ 6.8

*** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$; by paired *t*-test. Groups were formed by the end-diastolic diameter. Group 1: septal and/or posterior wall thickness ≥ 13 mm. Group 2: diastolic wall thickness is between 8–13 mm. Group 3: septal and/or posterior wall end diastolic diameter ≤ 8 mm. Abbreviations: MDD = mean disease duration (years); MA = mean age (years); AO = age at the onset $\pm$ s.d. (years); EDV = end diastolic volume; ESV = end systolic volume; SV = stroke volume; CO = cardiac output; EF = ejection fraction; FS = fractional shortening. Statistical differences between controls and patients, and between Groups 1 and 3 were calculated.

diastolic functions, the ratio of MIPT/MIET was significantly increased ($P<0.001$) in the patient's group as compared to the controls. Differences between patients and controls were also demonstrated in the A waves, and PFR/SV values (Table III).

Pericardial disease was found in 23 cases (28.7%). Pericardial thickening (>7 mm) was demonstrated in 14 (17.5%), and fluid in the pericardium was present in nine (11.2%) patients all of whom had less than 100 ml detected. In one patient, pericardial tamponade with 750 ml fluid was detected, and pericardiocentesis was performed. This particular case was excluded from the further studies.

Considering the systolic parameters of the diffuse and limited scleroderma groups, both of them showed impaired systolic functions as compared to controls, indicating that cases belonging to the limited SSc group also exhibit damaged left ventricular function in a significant proportion of patients (Table IV).

Discussion

There are two forms of scleroderma heart disease, the primary cardiac involvement and the secondary disorder due to hypertrophy caused by renal failure or other pulmonary disease.³¹ Scleroderma renal disease resulting in hypertension causes concentric left ventricular hypertrophy, when the impairment in diastolic function occurs first, and following the dilatation of cardiac chambers, left ventricular systolic functions become impaired also. In secondary cardiac disease in SSc, due to pulmonary fibrosis (and pulmonary hypertension), the right cardiac chambers and the diameter of the pulmonary artery become enlarged. These findings were registered by echocardiography in 45.7% of the cases showing the usefulness of echocardiography as a simple, noninvasive method for detecting right

Table IV Comparison of cardiac function of patients with diffuse and limited form of systemic sclerosis

	lcSSc	dcSSc	Controls
Number of cases	57	23	18
MDD (years)	9.6 ± 8.2	7.6 ± 7.5	—
AO (years)	39.5 ± 10.3	44.2 ± 13.6	—
SV (cm ³)	46.4 ± 14**	45.2 ± 12.5*	53.6 ± 8.1
EF (%)	46.2 ± 9.5*	42.8 ± 9.5**	51.7 ± 9.2
FS (%)	20.4 ± 6.1*	18 ± 6.3**	23.7 ± 6

** $P<0.01$; * $P<0.05$; by paired *t*-test. The lcSSc and dcSSc groups were compared to the controls. Abbreviations: lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis; MDD = mean disease duration; AO = age at the onset ± s.d.; SV = stroke volume; EF = ejection fraction; FS = fractional shortening.

ventricular overloading caused mainly by the lung involvement.

Primary cardiac involvement causes injury to different cardiac structures including the pericardium, conduction system and myocardium.^{5–27} Scleroderma pericardial disease includes effusion, and in the later stage, pericardial thickening which was also noted in our study. As primary myocardial involvement, myocardial fibrosis is often present in SSc. It is usually asymmetric, and therefore it can be differentiated from hypertrophic cardiomyopathy and necrosis of myocardium caused by coronary occlusion.^{5,22,31} Myocardial fibrosis was described in 48–81% of autopsy cases.^{5,9,22}

Based on the thickness of the septum and posterior wall, our patients were divided into three groups (Table II). Because of the correlation described above between the disease duration and wall thickness, our view is that an increase in the wall thickness may occur first as a sign of cardiac involvement, while at the later stages of disease,

Table III Diastolic functions of patients with different wall thickness in systemic sclerosis

	All cases	Controls	Group 1	Group 2	Group 3
Number of cases	80	18	15	40	25
HR	79.5 ± 12.8*	71.6 ± 11.8*	80.1 ± 12.8	77.1 ± 11.9	83 ± 14
A (m/second)	0.70 ± 0.19	0.62 ± 0.13	0.78 ± 0.24	0.7 ± 0.18	0.65 ± 0.18
MIPT/MIET	0.239 ± 0.29**	0.11 ± 0.13**	0.45 ± 0.47*	0.21 ± 0.25	0.16 ± 0.14*
PFR/SV	0.0081 ± 0.004	0.0069 ± 0.003	0.0053 ± 0.03**	0.0087 ± 0.005	0.0088 ± 0.05**

** $P<0.01$; * $P<0.05$; by paired *t*-test. Groups were formed by the end diastolic diameter. Group 1: septal and/or posterior wall thickness ≥ 13 mm. Group 2: diastolic wall thickness is between 8–13 mm. Group 3: septal and/or posterior wall end diastolic diameter ≤ 8 mm. Abbreviations: HR = heart rate; A = A wave; MIET = mitral Doppler duration time; MIPT = mitral Doppler acceleration time (peak time); PFR/SV = peak filling rate/stroke volume. Statistical differences between controls and patients, and between Groups 1 and 3 were calculated.

the wall tends to become thinner. Our results show that the disease duration should be taken into consideration when the cardiac function is being evaluated in SSc. Although we have no direct evidence, certain similarities may be present with the pathological events of the skin where the oedematous phase of the disease (with increased skin thickness) is followed by the fibrotic stage and finally by atrophy.³²

The three groups described above could be distinguished by certain parameters. In the group with increased asymmetric wall thickness, the end systolic wall thickening was minimal, the left ventricular volume parameters were increased, while the contractility parameters were slightly decreased, with the result that the cardiac output was not impaired, even though it was above the control values (Table II). The diastolic time was shortened, the acceleration time was relatively increased, while the deceleration was relatively decreased. The ratio of the peak filling rate to the stroke volume was decreased, showing the diastolic function impairment in this group (Table III). Therefore we concluded that these findings could not be explained by muscle hypertrophy of the myocardium. It seems to be a non-specific phenomenon caused possibly by intramyocardial oedema, inflammation and collagen deposition.

In Group 3, the mean disease duration was longer, and asymmetrical wall thinning was present. The diameters of the cardiac chambers tended to be increased, the left ventricular volume and contractility parameters were slightly decreased, the systolic wall thickening was increased, and the cardiac output was low (Table III). Impairment in the diastolic parameters were also present in this group. Although direct evidence is missing, it is tempting to speculate that these phenomena could possibly be caused by true cardiac fibrosis, which causes increased myocardial stiffness.

In the group with normal wall thickness, the functional systolic and diastolic parameters were slightly impaired, indicating that this group, beside the cases without cardiac involvement, also included patients with myocardial fibrosis.

The observed changes in the wall thickness, systolic and diastolic functions seem to be unrelated to other factors. These changes are not caused by hypertension, renal failure or an increased body weight of the patients. The ratio of the smokers was also low among the cases with SSc.

Our data are supported by the findings of Follansbee *et al.*¹³ For the detection of myocardial fibrosis a possible method is thallium exercise

scintigraphy. Follansbee *et al.* found an irreversible perfusion defect in 69% of patients with SSc, and 64% in the CREST variant. They also found systolic impairment by thallium scintigraphy in fibrotic cases, although they demonstrated a relatively preserved left ventricular function. The ejection fraction was impaired in 15% of the cases with diffuse scleroderma, while no reduced ejection fraction was detected in the CREST syndrome.¹³

Our findings are different from those of Kazzam *et al.*,^{16,33} because we found not only diastolic functional disturbances but systolic functional impairment in SSc as well. Their observations were based on the investigation of 30 patients with SSc, and the majority of their cases showed myocardial thickening.¹⁶ They found diastolic impairment in these cases. Like their findings, our hypertrophic cases (in Group 1) also showed serious diastolic impairment, but in our study, similar changes were also demonstrated in the other two groups of cases, although to a lesser extent. In the cases of Kazzam *et al.*, concentric hypertrophy was found to be a frequent finding (which may be due to hypertension or other secondary causes), while we found asymmetrical wall thickening. The female/male ratio was 1:1 in the study of Kazzam *et al.*, which is not characteristic of SSc, where the female/male ratio is generally much higher in this disease.¹² In another publication Kazzam *et al.* described systolic impairment of left ventricular function despite normal left ventricular dimensions.¹⁷ In our cases, we observed moderate changes in the cardiac output, fractional shortening and ejection fraction (Table II). These facts, including the different methods used (and perhaps geographical differences), could possibly explain the discrepancies between our findings.

In another study based on 10 patients, no impaired left ventricular systolic function was shown.¹¹ Patients in this study had mainly hypertrophy and left atrial enlargement. The findings are in agreement with those in our Group 1.

Our investigation shows that cardiac involvement is present in either limited or diffuse subgroups of patients with SSc and a relationship can be drawn between left ventricular wall thickness and the disease duration.

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