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Non-invasive assessment of systolic left ventricular function in systemic sclerosis

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Systemic sclerosis is a multisystemic disorder, also affecting the heart. To evaluate its influence on systolic left ventricular (LV) function, we investigated 30 consecutive patients (age 54·5±2·4 years, 15 men and 15 women) and 48 controls matched for age and sex. All subjects were investigated by phonocardiography, pulse curve recordings, M-mode echocardiography, and by pulsed and continuous wave Doppler. Heart rate, blood pressure and peripheral resistance did not differ, but patients weighed less than controls (P<0·01). Systolic time intervals indicated systolic impairment, with an increased pre-ejection period to LV ejection time (LVET) ratio (0·37±0·02 vs 0·30±0·01 P<0·001), and also an increased isovolumic contraction time to LVET ratio (0·17±0·02 vs 0·12±0·01, P<0·02). The latter difference remained when LVET was adjusted for heart rate. Echocardiographic E-point to septal separation was increased in patients (8·3±1·3 vs 4·8±0·3 mm, P=0·001), also after adjustment for LV dimension (P=0·0001), while septal fractional thickening was decreased (P<0·01). End systolic wall stress (P=0·0002) and stress to volume ratio (P=0·03) were lower in systemic sclerosis. Peak LV emptying rate was also lower in the patient group when measured by echocardiography (P=0·03). There was no difference between groups regarding LV dimensions, fractional shortening or mean velocity of circumferential fibre shortening. While aortic Doppler peak emptying rate did not differ between groups, it occurred later in systole in the patient group (P<0·01) as did peak velocity (P=0·0001). Cardiac output did not differ between the groups. In all, 18 of 30 patients (60%) had a systolic abnormality. However, only one patient had dilated cardiomyopathy, and two other patients had poor systolic function without LV dilatation. There was no relation between disease duration and systolic LV function.

We conclude that, in a consecutive series of patients with systemic sclerosis, systolic LV function is frequently impaired. While time intervals, emptying rate, and wall fractional thickening are affected, cardiac output and LV cavity dimensions are usually not.

Introduction

Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin. Visceral involvement is also well recognized, particularly the lungs, heart, kidneys and the gastrointestinal tract[1]. Cardiac involvement has, since it was reported by Weiss *et al.* in 1943[2], been a subject of wide interest[3–6]. Involvement of the heart in systemic sclerosis is associated with poor prognosis[7–8]. Since myocardial impairment may escape clinical detection, it seems important to apply methods with the potential to reveal cardiac dysfunction. However, results from non-invasive studies of systolic function in systemic sclerosis are somewhat contradictory[9,10].

We therefore studied a series of 30 consecutive patients to evaluate the presence and extent of left ventricular (LV) systolic dysfunction in systemic sclerosis and related the results to those of matched controls.

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Subjects and methods

SUBJECTS

We studied 30 consecutive patients (15 men and 15 women) with systemic sclerosis according to the American Rheumatology Association (ARA) criteria[11]. The patients were referred from The Uppsala region to Uppsala University Hospital between December 1986 and March 1988. Their mean age was 54·5 (range 25–77) years, and their disease had been recognized for 5·6 (range 0·5–23) years. General characteristics are shown in Table 1. Three randomly selected patients, and the patient with the largest reversible perfusion defect shown by myocardial scintigraphy after cold provocation, were subjected to coronary arteriography, but none of the four patients demonstrated abnormal angiograms. One patient had right bundle branch block, while none was found to have left bundle branch block.

For comparative purposes, age- and sex-matched control subjects were selected from the general population of Uppsala. Every resident in Sweden has a national registration number that includes date of birth. The numbers are registered by the County Census Bureau in a population register, which includes vital statistics, and which by law must be kept up to date. A sample of 90 age- and

Table 1 Characteristics of controls and patients

	Controls ($N=48$)	Patients ($N=30$)	P
Age (years)	54·6±2·1	54·5±2·4	N.S.
Sex (female/male)	22/26	15/15	N.S.
Height (cm)	172·7±1·11	170·9±1·9	N.S.
Weight (kg)	72·6±1·7	65·1±2·0	0·01
Body surface area (m^2)	1·9±0·03	1·7±0·04	0·02
Body mass index ($kg\ m^{-2}$)	24·3±0·5	22·3±0·9	0·008
Systolic blood pressure (mmHg)	134·9±2·6	132·9±3·5	N.S.
Diastolic blood pressure (mmHg)	81·4±1·4	78·7±2·1	N.S.
Mean arterial blood pressure (mmHg)	99·3±1·5	96·8±2·1	N.S.
Total peripheral resistance ($dyn.s.cm^{-5}$)	1604±59	1723±132	N.S.

Values are mean ±S.E. N.S. = not significant.

sex-matched subjects (three for each patient) was drawn from the register. All 90 controls were informed about the investigation protocol, and 55 of them gave their consent to participate in the study. Controls were excluded if treated for hypertension, and if clinical history or electrocardiography revealed coronary or rheumatic heart disease. Controls were not excluded on the basis of blood pressure level. No control had bundle branch block. None had known renal or pulmonary disease. Of the 55 subjects willing to participate, two were excluded due to previous antihypertensive treatment, one due to an electrocardiogram (ECG) indicating coronary heart disease, one due to a clinical history suggestive of ischaemic heart disease, two subjects because of a history of rheumatic heart disease, and one subject because of inadequate recordings. The remaining 48 subjects (26 men and 22 females) had a mean age of 54·6 (range 25–77) years and were included as a healthy control group.

METHODS

A standard 12-lead resting ECG, pulse curves and phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as previously described[12]. In brief, simultaneous carotid pulse tracing, ECG (standard lead II) and a phonocardiogram from the third left parasternal intercostal space, were recorded at 100 mm s^{-1} at the end of normal relaxed expiration with the subject in the supine position. Apexcardiographic registrations were obtained similarly, but with the patient lying in the left lateral position.

Blood pressure was recorded in the supine position after 30 min of rest, after pulse recordings and immediately before M-mode recordings. Standard sphygmomanometer technique was applied, and the mean of three readings was used. Systolic blood pressure was measured at phase one and diastolic blood pressure at the disappearance of Korotkoff sound-phase five[13].

Echocardiography was performed by means of a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2·5 or 3·5 MHz phased array transducer. Parasternal two-dimensional (2-D) echocardiographic views[14] were stored on VHS 0·5 inch video tapes by means of a Panasonic video recorder NV 8100. Two-D guided M-mode echocardiograms[15] were recorded on strip charts (Honeywell, 8100, dry Silver paper) at a speed of 50 $mm.s^{-1}$. These investigations were performed with the subject lying in the left lateral position.

To measure cardiac output[16,17], a Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record the aortic flow spectrum. A 2 MHz single crystal pulsed and continuous wave Doppler probe with a diameter of 13·7 mm was used. The examination was carried out with patients lying in the left lateral position using an apical approach. The area of the maximum LV apex pulsation was defined, and the transducer was placed slightly above, slightly below or directly over it. Both continous and pulsed wave Doppler spectrum were recorded, guided by the Doppler signal of valve closure and opening. The audible Doppler sound pattern from the blood flow was also used, and the transducer was manipulated until the best spectral display was obtained from the aortic flow. Strip chart recordings were obtained at a speed of 50 $mm.s^{-1}$.

MEASUREMENTS

All measuring points were agreed upon by two observers (E.K. and K.C.). One investigator (E.K.) carried out all interpretations after the recordings had been coded and mixed (by K.C.). Only beats with acceptable or good quality were used for measurements.

From M-mode echocardiographic recordings the measurements listed below were made on three beats (leading edge to leading edge method) according to the recommendations made by the American Society of Echocardiography[18], and the mean was used for further calculations. LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-diastole (the electrocardiographic Q wave), and at end-systole (the shortest distance between the septum and the posterior wall). M-mode echocardiographic dimensions and time intervals as well as amplitudes from pulse tracings were measured by means of a digitizing table-minicomputer system.

LV wall fractional thickening was calculated as septal and posterior wall systolic increase of thickness, respectively, divided by the corresponding diastolic thickness. Fractional shortening was defined as the difference between LV diastolic and systolic dimensions divided by the diastolic dimension. Ejection fraction was calculated according to the cube formula, for reasons discussed elsewhere[15]. Mean velocity of circumferential fibre shortening (mean Vcf) was calculated as fractional shortening divided by LV ejection time (LVET). Mean Vcf adjusted for heart rate (mean Vcf_c) was calculated as fractional shortening divided by LVET normalized by the square root of the cardiac cycle length in seconds[19]. Mitral E-point to septal separation (EPSS) was defined as the vertical distance (mean of five beats) between the E point of the anterior mitral leaflet and the ventricular septum[20,21]. EPSS was adjusted for end-diastolic LV dimension.

LV meridional end-systolic wall stress (ESWS) (10^3.dyn.cm^{-2}) was estimated as ESWS = (1·332 × pressure × D)/[4h × (1 + h/D)], where D represents LV end-systolic dimension and h stands for the mean of the septal and posterior wall end-systolic thickness[15,22]. Pressure was obtained by estimating end-systolic blood pressure from the carotid pulse tracing, where systolic and diastolic blood pressures were assigned to the peak and nadir of the carotid curve, respectively, and end-systolic blood pressure was estimated by linear interpolation to the height of the dicrotic notch[23]. End-systolic volume index (ESVI) was calculated as end-systolic volume/body surface area. As a measure of contractility, we also calculated the ratio ESWS/ESVI. The mean Vcf_c to be expected from the level of ESWS was calculated by means of the regression formula obtained from the relation between these two variables in the control group. The ratio between measured and expected mean Vcf_c was calculated as percentage (mean Vcf_c%).

From M-mode recordings, LV peak emptying rate as well as time from the electrocardiographic R-wave to peak emptying rate were measured by means of a digitizing table (Summagraphics ID-2CTR-TAB 17, Connecticut, U.S.A.) and a microcomputer (Professional-380, Digital Equipment Corp., U.S.A.), using an especially designed computer programme[15]. The same equipment was used for the evaluation of Doppler recordings. Measurements of aortic Doppler (pulsed and continuous) registrations were performed on five beats, and the mean value was used. Maximum LV emptying velocity was measured. Stroke volume was calculated as the velocity integral of pulsed Doppler systolic aortic flow, multiplied by the aortic area[24,25], where the latter was calculated at π(dimension/2)^2 from the aortic diameter (leading edge) just below the insertion of the aortic leaflets in parasternal 2-D echocardiographic projection.

Mean arterial pressure (MAP) was calculated according to the formula (systolic − diastolic blood pressure)/3 + diastolic blood pressure. Total peripheral resistance (TPR) was calculated according to the formula TPR = MAP × 1·33[60/Doppler cardiac output].

Measurements of pulse curve tracings were performed on five beats, and the mean values were used. The LVET, the electromechanical interval, the pre-ejection period (PEP) and the isovolumic contraction time (ICT), were measured as previously described, from the simultaneous recordings of the electrocardiographic lead II, the phonocardiogram and the carotid pulse tracing or apex-cardiogram[12]. Electromechanical interval and LVET were related to heart rate. LVET was therefore adjusted for heart according to the regression equation of the control group. The relative LVET was calculated as percentage of the expected normal LVET. PEP/LVET and ICT/LVET were calculated. Ratios in which LVET had been adjusted to heart rate 60 (LVET divided by square root of the cycle length in seconds) were also computed.

STATISTICAL ANALYSIS

Data are presented as mean ± standard error of the mean (SE). Unpaired two-sided t-test was used to compare differences between patients and controls. P values $< 0{\cdot}05$ were considered significant. For selected variables, abnormal values were defined by two standard deviations (SDs) of the control group.

Results

GENERAL CHARACTERISTICS

Clinical characteristics of the controls and the patients are shown in Table 1. In spite of similar heights, patients weighed less than controls as a group, and five patients had a low calculated body surface area. Blood pressure and TPR were similar in the two groups.

SYSTOLIC TIME INTERVALS

In the patient group, LVET was significantly shorter, and ICT as well as PEP were longer (Table 2). Also in the patient group, the ratios PEP/LVET and ICT/LVET were significantly higher, and differences remained when the LVET was adjusted for heart rate. Five patients had an increased PEP/LVET ratio.

ECHOCARDIOGRAPHY AND DOPPLER

When heart rate was measured during the echocardiographic investigation, patients had higher heart rates than controls (Table 3), but only one patient had a heart rate above the reference limit. Two patients had LV dilatation, but the mean values of end-diastolic and end-systolic LV internal dimensions did not differ between groups, nor did fractional shortening, mean Vcf or mean Vcf_c (Table 3). In spite of this, EPSS was larger in patients (increased in 26%). The difference regarding EPSS remained after adjustment for LV dimension. Septal fractioning thickening was reduced in systemic sclerosis, and stroke volume tended to be lower ($P = 0{\cdot}06$), as did stroke volume calculated from Doppler recordings (Table 4). ESWS was lower in the patient group (Table 3), and a difference remained when ESWS was adjusted for ESVI. Mean Vcf_c% tended to be lower in the patient group, and three patients had a reduced value. The peak rate of LV emptying, measured from M-mode echocardiography, was lower among patients (Table 3). The time from the

Table 2 Systolic time intervals

	Controls ($N=48$)	Patients ($N=30$)	P
LVET (ms)	323±4	303±6	0·007
PEP (ms)	96±3	110±5	0·01
ICT (ms)	40±3·2	51±4·2	0·04
PEP/LVET	0·30±0·01	0·37±0·02	0·0006
ICT/LVET	0·12±0·01	0·17±0·02	0·01
PEP/$LVET_c$	0·30±0·01	0·37±0·02	0·0006
ICT/$LVET_c$	0·12±0·01	0.17±0·02	0·01

Values are mean ±S.E. LVET=left ventricular ejection time; PEP=pre-ejection period; ICT=isovolumic contraction time; $LVET_c$=left ventricular time normalized for the square root of the cardiac cycle length.

Table 3 M-mode echocardiographic measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·6±1·4	67·5±1·7	0·01
LV dimension (Q) (mm)	49·9±0·8	48·5±1·4	N.S.
LV dimension (end-systole) (mm)	32·8±0·7	32·5±1·7	N.S.
Fractional thickening			
Septum (%)	43±3	30±4	0·007
Posterior wall (%)	61±4	53±5	N.S.
Stroke volume (ml)	94·5±4·9	80·4±5·0	N.S.
Ejection fraction	0·72±0·01	0·69±0·03	N.S.
Fractional shortening (%)	34·6±0·9	33·5±1·6	N.S.
Mean Vcf (circ s^{-1})	1·07±0·03	1·11±0·05	N.S.
Mean Vcf_c (circ s^{-1} $s^{0·5}$)	1·07±0·03	1·05±0·05	N.S.
Mean Vcf_c%	98·5±1·9	92·7±2·6	N.S.
ESWS (10^3.dyn.cm^{-2})	62·9±2·2	51·3±2·8	0·002
ESVI (ml m^{-2})	20·1±1·1	19·5±1·8	N.S.
ESWS/ESVI (10^3.dyn.cm^{-1}.ml^{-1}.cm^2)	3·34±0·13	2·9±0·16	0·03
EPSS (mm)	4·8±0·3	8·3±1·3	0·001
EPSS/LV dimension (Q)	0·098±0·01	0·162±0·02	0·0001
Peak emptying rate (mm s^{-2})	−105·5±4·2	−92·0±3·4	0·03
Time R wave to peak emptying rate (ms)	201·9±9·3	188·6±11·8	N.S.
Time to peak emptying (% of systole)	68·2±3·3	67·1±4·8	N.S.

Values are mean ±S.E. N.S.=not significant. LV=left ventricular; Vcf=velocity of circumferential fibre shortening; Vcf_c=Vcf adjusted for heart rate; Vcf_c%=measured/expected (from ESWS) Vcf_c; ESWS=end-systolic wall stress; ESVI=end-systolic volume index; EPSS=E-point septal separation.

R-wave to peak emptying did not differ, but, when calculated in relation to duration of systole, peak emptying occurred later in the patient group. When calculated from continuous wave Doppler (Table 4), the time to peak aortic flow acceleration, and also the time to peak aortic flow velocity, was longer in the patient group in spite of no significant difference regarding peak velocity of LV emptying (aortic flow acceleration) as calculated from Doppler.

INDIVIDUAL ABNORMALITIES

We evaluated the number of patients with abnormal values regarding the following variables: LV end-diastole dimension, ejection fraction, Vcf_c%, PEP/LVET, ICT/LVET, ESWS/ESVI, EPSS, time to peak aortic flow velocity and acceleration. Altogether, 18 patients (60%) had one or more abnormal findings regarding these variables. The variables displaying the highest prevalence of abnormal values were EPSS, time to peak flow velocity, PEP/LVET, and time to aortic peak flow acceleration. There was no significant relation between these variables and disease duration.

One patient had findings of dilated cardiomyopathy with a dilated left ventricle (77 mm) and a low ejection fraction (22%). Two other patients had low ejection fraction and low Vcf_c% in spite of LV dimension within the reference limits. Two patients had isolated abnormality of systolic time intervals and two patients isolated increase of EPSS.

Discussion

The present study is the first to compare LV function, in a consecutive series of patients with systemic sclerosis,

Table 4 Doppler measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·4±1·1	69·0±2·1	0·0008
Stroke volume (ml)	74·4±2·8	67·5±5·0	N.S.
Cardiac output (l min^{-1})	4·6±0·2	4·5±0·3	N.S.
Peak aortic gradient (mmHg)	5·3±0·4	5·0±0·5	N.S.
Time to peak velocity (% of systole)	25·0±0·8	31·7±1·6	0·0001
Peak acceleration (mmHg s^{-1})	111±6	104±11	N.S.
Time to peak acceleration (% of systole)	9·1±0·3	10·6±0·6	0·01

Values are mean ±S.E. N.S. = not significant.

with that of a random sample of matched control subjects from the general population. Great care was taken to ensure objective evaluation of data. Thus, the investigations were all carried out by the same investigator, who was unaware of the clinical findings. Interpretations were likewise performed by a single investigator, after blind-coding and mixing of the recordings from patients and controls.

Focal myocardial fibrosis reported by several authors[3,5,26], may be the reason for the development of myocardial dysfunction in systemic sclerosis. However, even patients with systemic sclerosis who died suddenly seem to display conspicuously normal extramural coronary arteries at autopsy[27,28]. Focal myocardial lesions have no relation to specific extramural vasculature[3], and myocardial necrosis occurs with widely patent intramural and extramural coronary arteries, suggesting the microcirculation is abnormal[28–30]. Although patients with arrhythmias and conduction disturbances who die suddenly have abnormalities of their sinus node artery and AV-node artery[27], an autopsy study of 52 patients have shown intramural coronary arteries to be generally normal histologically and microangiograms in 12 patients to be free from abnormalities[3]. Vasospasm or myocardial Raynaud's phenomenon have been suggested to be responsible for the myocardial necrosis seen in systemic sclerosis[28,29], and we were recently able to substantiate this hypothesis by showing in the present study group reversible myocardial perfusion defects induced by cold provocation[31]. Since in the patient with the largest myocardial perfusion defects arteriography showed normal coronary arteries, as did the angiograms from three randomly selected patients, we considered coronary arteriography to be neither necessary nor ethical in the remainder of the present study population. Moreover, we could not, for ethical reasons, have made comparative studies in the control group.

Some patients with systemic sclerosis develop severe cardiac involvement with a picture of dilated cardiomyopathy[32]. Such findings are, however, rare and were only seen in one patient in the present study, while two other patients had low ejection fraction without dilatation. Most patients had only a mild or moderate impairment of systolic function. Thus, the mean values of ejection fraction did not differ between the groups.

The systolic time intervals of the patients were clearly abnormal. One possible explanation for this is inclusion of patients with bundle branch block, while controls had normal transmission of depolarization potentials. Such an explanation was, however, not valid, since only one patient had right bundle branch block, and none had left bundle branch block. A more plausible explanation of abnormal systolic time intervals is obviously a true myocardial impairment.

The existence of myocardial dysfunction was substantiated by the findings of increased EPSS (with and without adjustment for LV dimension), reduced septal fractional thickening, reduced LV emptying by M-mode digitization, and delayed times to peak aortic flow acceleration and velocity by Doppler. The time for aortic flow to peak acceleration and velocity may be more sensitive indicators of contractility than peak acceleration, although also the latter tended to be abnormal.

We used EPSS in the present study since this measure has been shown to be a valid predictor of depressed systolic function independent of LV size and wall motion abnormalities, and better than other echocardiographic indices correlated to angiographic ejection fraction[20,33,34]. Mitral regurgitation causing a low afterload in the patient group is one possible explanation for the lack of difference between groups regarding fractional shortening and similar indices[35]. Although, Doppler evidence of mild mitral insufficiency was prevalent, moderate or severe regurgitation was rare (two patients) in systemic sclerosis (any degree of regurgitation found in 40% of patients vs 4% in the control group, $P<0·001$)[36], a low afterload being more probably explained by systolic impairment together with an increased relative wall thickness among patients[37]. The ratio ESWS/ESVI takes load into account, and a low value of this ratio indicates systolic impairment irrespective of mitral regurgitation[38]. Thus, the difference between groups regarding ESWS/ESVI means systolic impairment in the patient group.

We conclude that the systolic LV function in many patients with systemic sclerosis is impaired to a mild or moderate degree. The prevalence of more advanced involvement is low, possibly because of rapid deterioration in such cases. However, myocardial dysfunction seems to be detectable at an early stage when it could still be influenced by medical therapy. The cardiac effects of

treatment with angiotensin-converting-enzyme inhibitors is currently being evaluated in the present study population.

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References

[1] Medsger TA Jr. Systemic sclerosis (Scleroderma), eosinophilic fasciitis, and calcinosis. In: McCarthy DJ, Ed. Arthritis and allied conditions. A textbook of rheumatology. Philadelphia: Lea & Febiger, 1985, 994–1036.

[2] Weiss S, Stead EA, Warren JV, Bailey OT. Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma. Arch Intern Med 1943; 71: 749–76.

[3] Bulkley BH, Ridolfi RL, Slayer ER, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976; 53: 483–90.

[4] Mac Whorter JE, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). Am J Med 1974; 57: 566–75.

[5] Sackner MA, Heinz ER, Steinberg AJ. The heart in scleroderma. Am J Cardiol 1966; 17: 542–75.

[6] Gottdiener Moutsopoulos HM, Decker JL. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979; 66: 391–8.

[7] 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: 369–76.

[8] Orabona ML, Albino O. Systemic progressive sclerosis (or visceral scleroderma). Review of the literature and report of cases. Acta Med Scand 1958; 160 (Suppl): 160–70.

[9] Siegel RJ, O'Connor B, M Ena I, Criley JM. Left ventricular function at rest and during Raynaud's phenomenon in patients with scleroderma. Am Heart J 1984; 108: 1469–76.

[10] Gaffney FA, Anderson RJ, Nixon JV, Blomqvist CG, Moore Jr WE. Cardiovascular function in patients with progressive systemic sclerosis (scleroderma). Clin Cardiol 1982; 5: 569–76.

[11] Subcommittee for scleroderma criteria of American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581–90.

[12] Wikstrand J, Berglund G, Wilhelmsen L, Wallentin I. Value of systolic and diastolic time intervals. Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction. Br Heart J 1978; 40: 256–67.

[13] American Heart Association: Recommendation for human blood pressure. Determination by sphygmomanometer. Circulation 1980; 62: 1145A–55A.

[14] Caidahl K, Svärdsudd K, Eriksson H, Wilhelmsen L. Relation of dyspnea to left ventricular wall motion disturbances in a population of 67-year-old men. Am J Cardiol 1987; 59: 1277–82.

[15] Caidahl K, Eriksson H, Hartford M, Wikstrand J, Wallentin I, Svärdsudd K. Dyspnoea of cardiac origin in 67-year-old men: I. Relation to systolic left ventricular function and wall stress. The study of men born in 1913. Br Heart J 1988; 59: 319–28.

[16] Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiography determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425–31.

[17] Ihlen H, Pamile JP, Dale J *et al.* Determination of cardiac output by Doppler echocardiography. Br Heart J 1984; 51: 54–60.

[18] Sahn DJ, DeMaria A, Kisslo J, Weyman AI. The committee on M-mode standardization of the American Society of Echocardiology: Recommendation regarding quantitation in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation 1978; 58: 1072–8.

[19] Colan SD, Borow KM, Newmann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load independent index of myocardial contractility. J Am Coll Cardiol 1984; 4: 715–24.

[20] Lew W, Henning H, Schelbert H, Karliner JS. Assessment of mitral E point-septal separation as an index of left ventricular performance in patients with acute and previous myocardial infarction. Am J Cardiol 1978; 41: 836–45.

[21] Caidahl K, Svärdsudd K, Eriksson H *et al.* Dyspnea of cardiac origin in 67-year-old men: relation to clinical and non-invasive measures of cardiac function. Am J Noninv Cardiol 1988; 2: 59–68.

[22] Grossman W, Jones D, MacLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1987; 8: 384–94.

[23] Borow KM, Green LH, Grossman W, Branwald E. Left ventricular end-systolic stress shortening and stress-length relation in humans. Normal values and sensitivity inotropic state. Am J Cardiol 1982; 50: 1301–8.

[24] Hatle L, Angelsen B. Doppler ultrasound in cardiology: physical principles and clinical application. Second edition. Philadelphia: Lea & Febiger, 1986.

[25] Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. Pediatr Cardiol 1987; 8: 241–6.

[26] Leinwand I, Duryee AW, Richter MN. Scleroderma (based on a study of over 150 cases). Ann Intern Med 1954; 41: 1003–41.

[27] James TN. VIII. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974; 50: 844–56.

[28] Bulkley BH, Klacsmann PG, Hutchins GM. Angina pectoris, myocardial infarction and sudden cardiac death with normal coronary arteries: A clinicopathologic study of 9 patients with progressive systemic sclerosis. Am Heart J 1978; 95: 563–9.

[29] Follansbee WP, Curtiss EI, Medsger TA *et al.* Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N Engl J Med 1984; 310: 142–8.

[30] Kahan A, Nitenberg A, Foult JM *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985; 28: 637–45.

[31] Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. Lancet 1989; ii: 475–9.

[32] Eggebrecht RF, Kleiger RE. Echocardiographic pattern in scleroderma. Chest 1977; 71: 47–51.

[33] Child JS, Krivokapich J, Perloff JK. Effect of left ventricular size on mitral E point to ventricular septal separation in assessment of cardiac performance. Am Heart J 1981; 101: 797–804.

[34] Ahmadpour H, Shah AA, Allen JW *et al.* Mitral E point septal separation: a reliable index of left ventricular performance in coronary artery disease. Am Heart J 1983; 106: 21–8.

[35] Caidahl K, Larsson S, Südow G, Wallentin I, Angelhed J-E, Olsson SB. Conservative surgery for mitral valve prolapse with regurgitation: clinical follow-up and noninvasive assessment. Eur Heart J 1987; 8: 384–94.

[36] Kazzam E, Johansson C, Waldenström A, Hällgren R, Caidahl K. Doppler findings of mitral regurgitation and impaired left ventricular filling properties in systemic sclerosis. J Am Coll Cardiol 1990; 15 (Suppl): 273A (Abstr).

[37] Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in systemic sclerosis. J Int Med 1990; 228: 183–92.

[38] Carabello BA, Spann JF. The uses and limitations of end-systolic indexes of left ventricular function. Circulation 1984; 69: 1058–64.

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Non-invasive assessment of systolic left ventricular function in systemic sclerosis

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Systemic sclerosis is a multisystemic disorder, also affecting the heart. To evaluate its influence on systolic left ventricular (LV) function, we investigated 30 consecutive patients (age 54·5±2·4 years, 15 men and 15 women) and 48 controls matched for age and sex. All subjects were investigated by phonocardiography, pulse curve recordings, M-mode echocardiography, and by pulsed and continuous wave Doppler. Heart rate, blood pressure and peripheral resistance did not differ, but patients weighed less than controls (P<0·01). Systolic time intervals indicated systolic impairment, with an increased pre-ejection period to LV ejection time (LVET) ratio (0·37±0·02 vs 0·30±0·01 P<0·001), and also an increased isovolumic contraction time to LVET ratio (0·17±0·02 vs 0·12±0·01, P<0·02). The latter difference remained when LVET was adjusted for heart rate. Echocardiographic E-point to septal separation was increased in patients (8·3±1·3 vs 4·8±0·3 mm, P=0·001), also after adjustment for LV dimension (P=0·0001), while septal fractional thickening was decreased (P<0·01). End systolic wall stress (P=0·0002) and stress to volume ratio (P=0·03) were lower in systemic sclerosis. Peak LV emptying rate was also lower in the patient group when measured by echocardiography (P=0·03). There was no difference between groups regarding LV dimensions, fractional shortening or mean velocity of circumferential fibre shortening. While aortic Doppler peak emptying rate did not differ between groups, it occurred later in systole in the patient group (P<0·01) as did peak velocity (P=0·0001). Cardiac output did not differ between the groups. In all, 18 of 30 patients (60%) had a systolic abnormality. However, only one patient had dilated cardiomyopathy, and two other patients had poor systolic function without LV dilatation. There was no relation between disease duration and systolic LV function.

We conclude that, in a consecutive series of patients with systemic sclerosis, systolic LV function is frequently impaired. While time intervals, emptying rate, and wall fractional thickening are affected, cardiac output and LV cavity dimensions are usually not.

Introduction

Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin. Visceral involvement is also well recognized, particularly the lungs, heart, kidneys and the gastrointestinal tract[1]. Cardiac involvement has, since it was reported by Weiss *et al.* in 1943[2], been a subject of wide interest[3–6]. Involvement of the heart in systemic sclerosis is associated with poor prognosis[7–8]. Since myocardial impairment may escape clinical detection, it seems important to apply methods with the potential to reveal cardiac dysfunction. However, results from non-invasive studies of systolic function in systemic sclerosis are somewhat contradictory[9,10].

We therefore studied a series of 30 consecutive patients to evaluate the presence and extent of left ventricular (LV) systolic dysfunction in systemic sclerosis and related the results to those of matched controls.

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Subjects and methods

SUBJECTS

We studied 30 consecutive patients (15 men and 15 women) with systemic sclerosis according to the American Rheumatology Association (ARA) criteria[11]. The patients were referred from The Uppsala region to Uppsala University Hospital between December 1986 and March 1988. Their mean age was 54·5 (range 25–77) years, and their disease had been recognized for 5·6 (range 0·5–23) years. General characteristics are shown in Table 1. Three randomly selected patients, and the patient with the largest reversible perfusion defect shown by myocardial scintigraphy after cold provocation, were subjected to coronary arteriography, but none of the four patients demonstrated abnormal angiograms. One patient had right bundle branch block, while none was found to have left bundle branch block.

For comparative purposes, age- and sex-matched control subjects were selected from the general population of Uppsala. Every resident in Sweden has a national registration number that includes date of birth. The numbers are registered by the County Census Bureau in a population register, which includes vital statistics, and which by law must be kept up to date. A sample of 90 age- and

Table 1 Characteristics of controls and patients

	Controls ($N=48$)	Patients ($N=30$)	P
Age (years)	54·6±2·1	54·5±2·4	N.S.
Sex (female/male)	22/26	15/15	N.S.
Height (cm)	172·7±1·11	170·9±1·9	N.S.
Weight (kg)	72·6±1·7	65·1±2·0	0·01
Body surface area (m^2)	1·9±0·03	1·7±0·04	0·02
Body mass index ($kg\,m^{-2}$)	24·3±0·5	22·3±0·9	0·008
Systolic blood pressure (mmHg)	134·9±2·6	132·9±3·5	N.S.
Diastolic blood pressure (mmHg)	81·4±1·4	78·7±2·1	N.S.
Mean arterial blood pressure (mmHg)	99·3±1·5	96·8±2·1	N.S.
Total peripheral resistance ($dyn.s.cm^{-5}$)	1604±59	1723±132	N.S.

Values are mean ±S.E. N.S. = not significant.

sex-matched subjects (three for each patient) was drawn from the register. All 90 controls were informed about the investigation protocol, and 55 of them gave their consent to participate in the study. Controls were excluded if treated for hypertension, and if clinical history or electrocardiography revealed coronary or rheumatic heart disease. Controls were not excluded on the basis of blood pressure level. No control had bundle branch block. None had known renal or pulmonary disease. Of the 55 subjects willing to participate, two were excluded due to previous antihypertensive treatment, one due to an electrocardiogram (ECG) indicating coronary heart disease, one due to a clinical history suggestive of ischaemic heart disease, two subjects because of a history of rheumatic heart disease, and one subject because of inadequate recordings. The remaining 48 subjects (26 men and 22 females) had a mean age of 54·6 (range 25–77) years and were included as a healthy control group.

METHODS

A standard 12-lead resting ECG, pulse curves and phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as previously described[12]. In brief, simultaneous carotid pulse tracing, ECG (standard lead II) and a phonocardiogram from the third left parasternal intercostal space, were recorded at 100 mm s^{-1} at the end of normal relaxed expiration with the subject in the supine position. Apex-cardiographic registrations were obtained similarly, but with the patient lying in the left lateral position.

Blood pressure was recorded in the supine position after 30 min of rest, after pulse recordings and immediately before M-mode recordings. Standard sphygmomanometer technique was applied, and the mean of three readings was used. Systolic blood pressure was measured at phase one and diastolic blood pressure at the disappearance of Korotkoff sound-phase five[13].

Echocardiography was performed by means of a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2·5 or 3·5 MHz phased array transducer. Parasternal two-dimensional (2-D) echocardiographic views[14] were stored on VHS 0·5 inch video tapes by means of a Panasonic video recorder NV 8100. Two-D guided M-mode echocardiograms[15] were recorded on strip charts (Honeywell, 8100, dry Silver paper) at a speed of 50 $mm.s^{-1}$. These investigations were performed with the subject lying in the left lateral position.

To measure cardiac output[16,17], a Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record the aortic flow spectrum. A 2 MHz single crystal pulsed and continuous wave Doppler probe with a diameter of 13·7 mm was used. The examination was carried out with patients lying in the left lateral position using an apical approach. The area of the maximum LV apex pulsation was defined, and the transducer was placed slightly above, slightly below or directly over it. Both continous and pulsed wave Doppler spectrum were recorded, guided by the Doppler signal of valve closure and opening. The audible Doppler sound pattern from the blood flow was also used, and the transducer was manipulated until the best spectral display was obtained from the aortic flow. Strip chart recordings were obtained at a speed of 50 $mm.s^{-1}$.

MEASUREMENTS

All measuring points were agreed upon by two observers (E.K. and K.C.). One investigator (E.K.) carried out all interpretations after the recordings had been coded and mixed (by K.C.). Only beats with acceptable or good quality were used for measurements.

From M-mode echocardiographic recordings the measurements listed below were made on three beats (leading edge to leading edge method) according to the recommendations made by the American Society of Echocardiography[18], and the mean was used for further calculations. LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-diastole (the electrocardiographic Q wave), and at end-systole (the shortest distance between the septum and the posterior wall). M-mode echocardiographic dimensions and time intervals as well as amplitudes from pulse tracings were measured by means of a digitizing table-minicomputer system.

LV wall fractional thickening was calculated as septal and posterior wall systolic increase of thickness, respectively, divided by the corresponding diastolic thickness. Fractional shortening was defined as the difference between LV diastolic and systolic dimensions divided by the diastolic dimension. Ejection fraction was calculated according to the cube formula, for reasons discussed elsewhere[15]. Mean velocity of circumferential fibre shortening (mean Vcf) was calculated as fractional shortening divided by LV ejection time (LVET). Mean Vcf adjusted for heart rate (mean Vcf_c) was calculated as fractional shortening divided by LVET normalized by the square root of the cardiac cycle length in seconds[19]. Mitral E-point to septal separation (EPSS) was defined as the vertical distance (mean of five beats) between the E point of the anterior mitral leaflet and the ventricular septum[20,21]. EPSS was adjusted for end-diastolic LV dimension.

LV meridional end-systolic wall stress (ESWS) (10^3.dyn.cm^{-2}) was estimated as ESWS = (1·332 × pressure × D)/[4h × (1 + h/D)], where D represents LV end-systolic dimension and h stands for the mean of the septal and posterior wall end-systolic thickness[15,22]. Pressure was obtained by estimating end-systolic blood pressure from the carotid pulse tracing, where systolic and diastolic blood pressures were assigned to the peak and nadir of the carotid curve, respectively, and end-systolic blood pressure was estimated by linear interpolation to the height of the dicrotic notch[23]. End-systolic volume index (ESVI) was calculated as end-systolic volume/body surface area. As a measure of contractility, we also calculated the ratio ESWS/ESVI. The mean Vcf_c to be expected from the level of ESWS was calculated by means of the regression formula obtained from the relation between these two variables in the control group. The ratio between measured and expected mean Vcf_c was calculated as percentage (mean Vcf_c%).

From M-mode recordings, LV peak emptying rate as well as time from the electrocardiographic R-wave to peak emptying rate were measured by means of a digitizing table (Summagraphics ID-2CTR-TAB 17, Connecticut, U.S.A.) and a microcomputer (Professional-380, Digital Equipment Corp., U.S.A.), using an especially designed computer programme[15]. The same equipment was used for the evaluation of Doppler recordings. Measurements of aortic Doppler (pulsed and continuous) registrations were performed on five beats, and the mean value was used. Maximum LV emptying velocity was measured. Stroke volume was calculated as the velocity integral of pulsed Doppler systolic aortic flow, multiplied by the aortic area[24,25], where the latter was calculated at π(dimension/2)^2 from the aortic diameter (leading edge) just below the insertion of the aortic leaflets in parasternal 2-D echocardiographic projection.

Mean arterial pressure (MAP) was calculated according to the formula (systolic − diastolic blood pressure)/3 + diastolic blood pressure. Total peripheral resistance (TPR) was calculated according to the formula TPR = MAP × 1·33[60/Doppler cardiac output].

Measurements of pulse curve tracings were performed on five beats, and the mean values were used. The LVET, the electromechanical interval, the pre-ejection period (PEP) and the isovolumic contraction time (ICT), were measured as previously described, from the simultaneous recordings of the electrocardiographic lead II, the phonocardiogram and the carotid pulse tracing or apexcardiogram[12]. Electromechanical interval and LVET were related to heart rate. LVET was therefore adjusted for heart according to the regression equation of the control group. The relative LVET was calculated as percentage of the expected normal LVET. PEP/LVET and ICT/LVET were calculated. Ratios in which LVET had been adjusted to heart rate 60 (LVET divided by square root of the cycle length in seconds) were also computed.

STATISTICAL ANALYSIS

Data are presented as mean ± standard error of the mean (SE). Unpaired two-sided t-test was used to compare differences between patients and controls. P values $< 0·05$ were considered significant. For selected variables, abnormal values were defined by two standard deviations (SDs) of the control group.

Results

GENERAL CHARACTERISTICS

Clinical characteristics of the controls and the patients are shown in Table 1. In spite of similar heights, patients weighed less than controls as a group, and five patients had a low calculated body surface area. Blood pressure and TPR were similar in the two groups.

SYSTOLIC TIME INTERVALS

In the patient group, LVET was significantly shorter, and ICT as well as PEP were longer (Table 2). Also in the patient group, the ratios PEP/LVET and ICT/LVET were significantly higher, and differences remained when the LVET was adjusted for heart rate. Five patients had an increased PEP/LVET ratio.

ECHOCARDIOGRAPHY AND DOPPLER

When heart rate was measured during the echocardiographic investigation, patients had higher heart rates than controls (Table 3), but only one patient had a heart rate above the reference limit. Two patients had LV dilatation, but the mean values of end-diastolic and end-systolic LV internal dimensions did not differ between groups, nor did fractional shortening, mean Vcf or mean Vcf_c (Table 3). In spite of this, EPSS was larger in patients (increased in 26%). The difference regarding EPSS remained after adjustment for LV dimension. Septal fractioning thickening was reduced in systemic sclerosis, and stroke volume tended to be lower ($P = 0·06$), as did stroke volume calculated from Doppler recordings (Table 4). ESWS was lower in the patient group (Table 3), and a difference remained when ESWS was adjusted for ESVI. Mean Vcf_c% tended to be lower in the patient group, and three patients had a reduced value. The peak rate of LV emptying, measured from M-mode echocardiography, was lower among patients (Table 3). The time from the

Table 2 Systolic time intervals

	Controls ($N=48$)	Patients ($N=30$)	P
LVET (ms)	323±4	303±6	0·007
PEP (ms)	96±3	110±5	0·01
ICT (ms)	40±3·2	51±4·2	0·04
PEP/LVET	0·30±0·01	0·37±0·02	0·0006
ICT/LVET	0·12±0·01	0·17±0·02	0·01
PEP/LVET$_c$	0·30±0·01	0·37±0·02	0·0006
ICT/LVET$_c$	0·12±0·01	0.17±0·02	0·01

Values are mean ±S.E. LVET=left ventricular ejection time; PEP=pre-ejection period; ICT=isovolumic contraction time; LVET$_c$=left ventricular time normalized for the square root of the cardiac cycle length.

Table 3 M-mode echocardiographic measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·6±1·4	67·5±1·7	0·01
LV dimension (Q) (mm)	49·9±0·8	48·5±1·4	N.S.
LV dimension (end-systole) (mm)	32·8±0·7	32·5±1·7	N.S.
Fractional thickening			
Septum (%)	43±3	30±4	0·007
Posterior wall (%)	61±4	53±5	N.S.
Stroke volume (ml)	94·5±4·9	80·4±5·0	N.S.
Ejection fraction	0·72±0·01	0·69±0·03	N.S.
Fractional shortening (%)	34·6±0·9	33·5±1·6	N.S.
Mean Vcf (circ s^{-1})	1·07±0·03	1·11±0·05	N.S.
Mean Vcf$_c$ (circ s^{-1} s$^{0·5}$)	1·07±0·03	1·05±0·05	N.S.
Mean Vcf$_c$%	98·5±1·9	92·7±2·6	N.S.
ESWS (10^3.dyn.cm^{-2})	62·9±2·2	51·3±2·8	0·002
ESVI (ml m^{-2})	20·1±1·1	19·5±1·8	N.S.
ESWS/ESVI (10^3.dyn.cm^{-1}.ml^{-1}.cm^2)	3·34±0·13	2·9±0·16	0·03
EPSS (mm)	4·8±0·3	8·3±1·3	0·001
EPSS/LV dimension (Q)	0·098±0·01	0·162±0·02	0·0001
Peak emptying rate (mm s^{-2})	−105·5±4·2	−92·0±3·4	0·03
Time R wave to peak emptying rate (ms)	201·9±9·3	188·6±11·8	N.S.
Time to peak emptying (% of systole)	68·2±3·3	67·1±4·8	N.S.

Values are mean ±S.E. N.S.=not significant. LV=left ventricular; Vcf=velocity of circumferential fibre shortening; Vcf$_c$=Vcf adjusted for heart rate; Vcf$_c$%=measured/expected (from ESWS) Vcf$_c$; ESWS=end-systolic wall stress; ESVI=end-systolic volume index; EPSS=E-point septal separation.

R-wave to peak emptying did not differ, but, when calculated in relation to duration of systole, peak emptying occurred later in the patient group. When calculated from continuous wave Doppler (Table 4), the time to peak aortic flow acceleration, and also the time to peak aortic flow velocity, was longer in the patient group in spite of no significant difference regarding peak velocity of LV emptying (aortic flow acceleration) as calculated from Doppler.

INDIVIDUAL ABNORMALITIES

We evaluated the number of patients with abnormal values regarding the following variables: LV end-diastole dimension, ejection fraction, Vcf$_c$%, PEP/LVET, ICT/LVET, ESWS/ESVI, EPSS, time to peak aortic flow velocity and acceleration. Altogether, 18 patients (60%) had one or more abnormal findings regarding these variables. The variables displaying the highest prevalence of abnormal values were EPSS, time to peak flow velocity, PEP/LVET, and time to aortic peak flow acceleration. There was no significant relation between these variables and disease duration.

One patient had findings of dilated cardiomyopathy with a dilated left ventricle (77 mm) and a low ejection fraction (22%). Two other patients had low ejection fraction and low Vcf$_c$% in spite of LV dimension within the reference limits. Two patients had isolated abnormality of systolic time intervals and two patients isolated increase of EPSS.

Discussion

The present study is the first to compare LV function, in a consecutive series of patients with systemic sclerosis,

Table 4 Doppler measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·4±1·1	69·0±2·1	0·0008
Stroke volume (ml)	74·4±2·8	67·5±5·0	N.S.
Cardiac output (l min^{-1})	4·6±0·2	4·5±0·3	N.S.
Peak aortic gradient (mmHg)	5·3±0·4	5·0±0·5	N.S.
Time to peak velocity (% of systole)	25·0±0·8	31·7±1·6	0·0001
Peak acceleration (mmHg s^{-1})	111±6	104±11	N.S.
Time to peak acceleration (% of systole)	9·1±0·3	10·6±0·6	0·01

Values are mean ±S.E. N.S. = not significant.

with that of a random sample of matched control subjects from the general population. Great care was taken to ensure objective evaluation of data. Thus, the investigations were all carried out by the same investigator, who was unaware of the clinical findings. Interpretations were likewise performed by a single investigator, after blind-coding and mixing of the recordings from patients and controls.

Focal myocardial fibrosis reported by several authors[3,5,26], may be the reason for the development of myocardial dysfunction in systemic sclerosis. However, even patients with systemic sclerosis who died suddenly seem to display conspicuously normal extramural coronary arteries at autopsy[27,28]. Focal myocardial lesions have no relation to specific extramural vasculature[3], and myocardial necrosis occurs with widely patent intramural and extramural coronary arteries, suggesting the microcirculation is abnormal[28–30]. Although patients with arrhythmias and conduction disturbances who die suddenly have abnormalities of their sinus node artery and AV-node artery[27], an autopsy study of 52 patients have shown intramural coronary arteries to be generally normal histologically and microangiograms in 12 patients to be free from abnormalities[3]. Vasospasm or myocardial Raynaud's phenomenon have been suggested to be responsible for the myocardial necrosis seen in systemic sclerosis[28,29], and we were recently able to substantiate this hypothesis by showing in the present study group reversible myocardial perfusion defects induced by cold provocation[31]. Since in the patient with the largest myocardial perfusion defects arteriography showed normal coronary arteries, as did the angiograms from three randomly selected patients, we considered coronary arteriography to be neither necessary nor ethical in the remainder of the present study population. Moreover, we could not, for ethical reasons, have made comparative studies in the control group.

Some patients with systemic sclerosis develop severe cardiac involvement with a picture of dilated cardiomyopathy[32]. Such findings are, however, rare and were only seen in one patient in the present study, while two other patients had low ejection fraction without dilatation. Most patients had only a mild or moderate impairment of systolic function. Thus, the mean values of ejection fraction did not differ between the groups.

The systolic time intervals of the patients were clearly abnormal. One possible explanation for this is inclusion of patients with bundle branch block, while controls had normal transmission of depolarization potentials. Such an explanation was, however, not valid, since only one patient had right bundle branch block, and none had left bundle branch block. A more plausible explanation of abnormal systolic time intervals is obviously a true myocardial impairment.

The existence of myocardial dysfunction was substantiated by the findings of increased EPSS (with and without adjustment for LV dimension), reduced septal fractional thickening, reduced LV emptying by M-mode digitization, and delayed times to peak aortic flow acceleration and velocity by Doppler. The time for aortic flow to peak acceleration and velocity may be more sensitive indicators of contractility than peak acceleration, although also the latter tended to be abnormal.

We used EPSS in the present study since this measure has been shown to be a valid predictor of depressed systolic function independent of LV size and wall motion abnormalities, and better than other echocardiographic indices correlated to angiographic ejection fraction[20,33,34]. Mitral regurgitation causing a low afterload in the patient group is one possible explanation for the lack of difference between groups regarding fractional shortening and similar indices[35]. Although, Doppler evidence of mild mitral insufficiency was prevalent, moderate or severe regurgitation was rare (two patients) in systemic sclerosis (any degree of regurgitation found in 40% of patients vs 4% in the control group, $P<0·001$)[36], a low afterload being more probably explained by systolic impairment together with an increased relative wall thickness among patients[37]. The ratio ESWS/ESVI takes load into account, and a low value of this ratio indicates systolic impairment irrespective of mitral regurgitation[38]. Thus, the difference between groups regarding ESWS/ESVI means systolic impairment in the patient group.

We conclude that the systolic LV function in many patients with systemic sclerosis is impaired to a mild or moderate degree. The prevalence of more advanced involvement is low, possibly because of rapid deterioration in such cases. However, myocardial dysfunction seems to be detectable at an early stage when it could still be influenced by medical therapy. The cardiac effects of

treatment with angiotensin-converting-enzyme inhibitors is currently being evaluated in the present study population.

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References

[1] Medsger TA Jr. Systemic sclerosis (Scleroderma), eosinophilic fasciitis, and calcinosis. In: McCarthy DJ, Ed. Arthritis and allied conditions. A textbook of rheumatology. Philadelphia: Lea & Febiger, 1985, 994–1036.

[2] Weiss S, Stead EA, Warren JV, Bailey OT. Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma. Arch Intern Med 1943; 71: 749–76.

[3] Bulkley BH, Ridolfi RL, Slayer ER, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976; 53: 483–90.

[4] Mac Whorter JE, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). Am J Med 1974; 57: 566–75.

[5] Sackner MA, Heinz ER, Steinberg AJ. The heart in scleroderma. Am J Cardiol 1966; 17: 542–75.

[6] Gottdiener Moutsopoulos HM, Decker JL. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979; 66: 391–8.

[7] 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: 369–76.

[8] Orabona ML, Albino O. Systemic progressive sclerosis (or visceral scleroderma). Review of the literature and report of cases. Acta Med Scand 1958; 160 (Suppl): 160–70.

[9] Siegel RJ, O'Connor B, M Ena I, Criley JM. Left ventricular function at rest and during Raynaud's phenomenon in patients with scleroderma. Am Heart J 1984; 108: 1469–76.

[10] Gaffney FA, Anderson RJ, Nixon JV, Blomqvist CG, Moore Jr WE. Cardiovascular function in patients with progressive systemic sclerosis (scleroderma). Clin Cardiol 1982; 5: 569–76.

[11] Subcommittee for scleroderma criteria of American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581–90.

[12] Wikstrand J, Berglund G, Wilhelmsen L, Wallentin I. Value of systolic and diastolic time intervals. Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction. Br Heart J 1978; 40: 256–67.

[13] American Heart Association: Recommendation for human blood pressure. Determination by sphygmomanometer. Circulation 1980; 62: 1145A–55A.

[14] Caidahl K, Svärdsudd K, Eriksson H, Wilhelmsen L. Relation of dyspnea to left ventricular wall motion disturbances in a population of 67-year-old men. Am J Cardiol 1987; 59: 1277–82.

[15] Caidahl K, Eriksson H, Hartford M, Wikstrand J, Wallentin I, Svärdsudd K. Dyspnoea of cardiac origin in 67-year-old men: I. Relation to systolic left ventricular function and wall stress. The study of men born in 1913. Br Heart J 1988; 59: 319–28.

[16] Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiography determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425–31.

[17] Ihlen H, Pamile JP, Dale J *et al.* Determination of cardiac output by Doppler echocardiography. Br Heart J 1984; 51: 54–60.

[18] Sahn DJ, DeMaria A, Kisslo J, Weyman AI. The committee on M-mode standardization of the American Society of Echocardiology: Recommendation regarding quantitation in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation 1978; 58: 1072–8.

[19] Colan SD, Borow KM, Newmann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load independent index of myocardial contractility. J Am Coll Cardiol 1984; 4: 715–24.

[20] Lew W, Henning H, Schelbert H, Karliner JS. Assessment of mitral E point-septal separation as an index of left ventricular performance in patients with acute and previous myocardial infarction. Am J Cardiol 1978; 41: 836–45.

[21] Caidahl K, Svärdsudd K, Eriksson H *et al.* Dyspnea of cardiac origin in 67-year-old men: relation to clinical and non-invasive measures of cardiac function. Am J Noninv Cardiol 1988; 2: 59–68.

[22] Grossman W, Jones D, MacLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1987; 8: 384–94.

[23] Borow KM, Green LH, Grossman W, Branwald E. Left ventricular end-systolic stress shortening and stress-length relation in humans. Normal values and sensitivity inotropic state. Am J Cardiol 1982; 50: 1301–8.

[24] Hatle L, Angelsen B. Doppler ultrasound in cardiology: physical principles and clinical application. Second edition. Philadelphia: Lea & Febiger, 1986.

[25] Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. Pediatr Cardiol 1987; 8: 241–6.

[26] Leinwand I, Duryee AW, Richter MN. Scleroderma (based on a study of over 150 cases). Ann Intern Med 1954; 41: 1003–41.

[27] James TN. VIII. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974; 50: 844–56.

[28] Bulkley BH, Klacsmann PG, Hutchins GM. Angina pectoris, myocardial infarction and sudden cardiac death with normal coronary arteries: A clinicopathologic study of 9 patients with progressive systemic sclerosis. Am Heart J 1978; 95: 563–9.

[29] Follansbee WP, Curtiss EI, Medsger TA *et al.* Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N Engl J Med 1984; 310: 142–8.

[30] Kahan A, Nitenberg A, Foult JM *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985; 28: 637–45.

[31] Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. Lancet 1989; ii: 475–9.

[32] Eggebrecht RF, Kleiger RE. Echocardiographic pattern in scleroderma. Chest 1977; 71: 47–51.

[33] Child JS, Krivokapich J, Perloff JK. Effect of left ventricular size on mitral E point to ventricular septal separation in assessment of cardiac performance. Am Heart J 1981; 101: 797–804.

[34] Ahmadpour H, Shah AA, Allen JW *et al.* Mitral E point septal separation: a reliable index of left ventricular performance in coronary artery disease. Am Heart J 1983; 106: 21–8.

[35] Caidahl K, Larsson S, Südow G, Wallentin I, Angelhed J-E, Olsson SB. Conservative surgery for mitral valve prolapse with regurgitation: clinical follow-up and noninvasive assessment. Eur Heart J 1987; 8: 384–94.

[36] Kazzam E, Johansson C, Waldenström A, Hällgren R, Caidahl K. Doppler findings of mitral regurgitation and impaired left ventricular filling properties in systemic sclerosis. J Am Coll Cardiol 1990; 15 (Suppl): 273A (Abstr).

[37] Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in systemic sclerosis. J Int Med 1990; 228: 183–92.

[38] Carabello BA, Spann JF. The uses and limitations of end-systolic indexes of left ventricular function. Circulation 1984; 69: 1058–64.

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Non-invasive assessment of systolic left ventricular function in systemic sclerosis

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KEY WORDS: Doppler, echocardiography, left ventricle, systemic sclerosis, systolic function, time intervals, wall stress.

Systemic sclerosis is a multisystemic disorder, also affecting the heart. To evaluate its influence on systolic left ventricular (LV) function, we investigated 30 consecutive patients (age 54·5±2·4 years, 15 men and 15 women) and 48 controls matched for age and sex. All subjects were investigated by phonocardiography, pulse curve recordings, M-mode echocardiography, and by pulsed and continuous wave Doppler. Heart rate, blood pressure and peripheral resistance did not differ, but patients weighed less than controls (P<0·01). Systolic time intervals indicated systolic impairment, with an increased pre-ejection period to LV ejection time (LVET) ratio (0·37±0·02 vs 0·30±0·01 P<0·001), and also an increased isovolumic contraction time to LVET ratio (0·17±0·02 vs 0·12±0·01, P<0·02). The latter difference remained when LVET was adjusted for heart rate. Echocardiographic E-point to septal separation was increased in patients (8·3±1·3 vs 4·8±0·3 mm, P=0·001), also after adjustment for LV dimension (P=0·0001), while septal fractional thickening was decreased (P<0·01). End systolic wall stress (P=0·0002) and stress to volume ratio (P=0·03) were lower in systemic sclerosis. Peak LV emptying rate was also lower in the patient group when measured by echocardiography (P=0·03). There was no difference between groups regarding LV dimensions, fractional shortening or mean velocity of circumferential fibre shortening. While aortic Doppler peak emptying rate did not differ between groups, it occurred later in systole in the patient group (P<0·01) as did peak velocity (P=0·0001). Cardiac output did not differ between the groups. In all, 18 of 30 patients (60%) had a systolic abnormality. However, only one patient had dilated cardiomyopathy, and two other patients had poor systolic function without LV dilatation. There was no relation between disease duration and systolic LV function.

We conclude that, in a consecutive series of patients with systemic sclerosis, systolic LV function is frequently impaired. While time intervals, emptying rate, and wall fractional thickening are affected, cardiac output and LV cavity dimensions are usually not.

Introduction

Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin. Visceral involvement is also well recognized, particularly the lungs, heart, kidneys and the gastrointestinal tract[1]. Cardiac involvement has, since it was reported by Weiss *et al.* in 1943[2], been a subject of wide interest[3–6]. Involvement of the heart in systemic sclerosis is associated with poor prognosis[7–8]. Since myocardial impairment may escape clinical detection, it seems important to apply methods with the potential to reveal cardiac dysfunction. However, results from non-invasive studies of systolic function in systemic sclerosis are somewhat contradictory[9,10].

We therefore studied a series of 30 consecutive patients to evaluate the presence and extent of left ventricular (LV) systolic dysfunction in systemic sclerosis and related the results to those of matched controls.

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Subjects and methods

SUBJECTS

We studied 30 consecutive patients (15 men and 15 women) with systemic sclerosis according to the American Rheumatology Association (ARA) criteria[11]. The patients were referred from The Uppsala region to Uppsala University Hospital between December 1986 and March 1988. Their mean age was 54·5 (range 25–77) years, and their disease had been recognized for 5·6 (range 0·5–23) years. General characteristics are shown in Table 1. Three randomly selected patients, and the patient with the largest reversible perfusion defect shown by myocardial scintigraphy after cold provocation, were subjected to coronary arteriography, but none of the four patients demonstrated abnormal angiograms. One patient had right bundle branch block, while none was found to have left bundle branch block.

For comparative purposes, age- and sex-matched control subjects were selected from the general population of Uppsala. Every resident in Sweden has a national registration number that includes date of birth. The numbers are registered by the County Census Bureau in a population register, which includes vital statistics, and which by law must be kept up to date. A sample of 90 age- and

Table 1 Characteristics of controls and patients

	Controls ($N=48$)	Patients ($N=30$)	P
Age (years)	54·6±2·1	54·5±2·4	N.S.
Sex (female/male)	22/26	15/15	N.S.
Height (cm)	172·7±1·11	170·9±1·9	N.S.
Weight (kg)	72·6±1·7	65·1±2·0	0·01
Body surface area (m^2)	1·9±0·03	1·7±0·04	0·02
Body mass index ($kg\ m^{-2}$)	24·3±0·5	22·3±0·9	0·008
Systolic blood pressure (mmHg)	134·9±2·6	132·9±3·5	N.S.
Diastolic blood pressure (mmHg)	81·4±1·4	78·7±2·1	N.S.
Mean arterial blood pressure (mmHg)	99·3±1·5	96·8±2·1	N.S.
Total peripheral resistance ($dyn.s.cm^{-5}$)	1604±59	1723±132	N.S.

Values are mean ±S.E. N.S. = not significant.

sex-matched subjects (three for each patient) was drawn from the register. All 90 controls were informed about the investigation protocol, and 55 of them gave their consent to participate in the study. Controls were excluded if treated for hypertension, and if clinical history or electrocardiography revealed coronary or rheumatic heart disease. Controls were not excluded on the basis of blood pressure level. No control had bundle branch block. None had known renal or pulmonary disease. Of the 55 subjects willing to participate, two were excluded due to previous antihypertensive treatment, one due to an electrocardiogram (ECG) indicating coronary heart disease, one due to a clinical history suggestive of ischaemic heart disease, two subjects because of a history of rheumatic heart disease, and one subject because of inadequate recordings. The remaining 48 subjects (26 men and 22 females) had a mean age of 54·6 (range 25–77) years and were included as a healthy control group.

METHODS

A standard 12-lead resting ECG, pulse curves and phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as previously described[12]. In brief, simultaneous carotid pulse tracing, ECG (standard lead II) and a phonocardiogram from the third left parasternal intercostal space, were recorded at 100 mm s^{-1} at the end of normal relaxed expiration with the subject in the supine position. Apexcardiographic registrations were obtained similarly, but with the patient lying in the left lateral position.

Blood pressure was recorded in the supine position after 30 min of rest, after pulse recordings and immediately before M-mode recordings. Standard sphygmomanometer technique was applied, and the mean of three readings was used. Systolic blood pressure was measured at phase one and diastolic blood pressure at the disappearance of Korotkoff sound-phase five[13].

Echocardiography was performed by means of a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2·5 or 3·5 MHz phased array transducer. Parasternal two-dimensional (2-D) echocardiographic views[14] were stored on VHS 0·5 inch video tapes by means of a Panasonic video recorder NV 8100. Two-D guided M-mode echocardiograms[15] were recorded on strip charts (Honeywell, 8100, dry Silver paper) at a speed of 50 mm.s^{-1}. These investigations were performed with the subject lying in the left lateral position.

To measure cardiac output[16,17], a Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record the aortic flow spectrum. A 2 MHz single crystal pulsed and continuous wave Doppler probe with a diameter of 13·7 mm was used. The examination was carried out with patients lying in the left lateral position using an apical approach. The area of the maximum LV apex pulsation was defined, and the transducer was placed slightly above, slightly below or directly over it. Both continous and pulsed wave Doppler spectrum were recorded, guided by the Doppler signal of valve closure and opening. The audible Doppler sound pattern from the blood flow was also used, and the transducer was manipulated until the best spectral display was obtained from the aortic flow. Strip chart recordings were obtained at a speed of 50 mm.s^{-1}.

MEASUREMENTS

All measuring points were agreed upon by two observers (E.K. and K.C.). One investigator (E.K.) carried out all interpretations after the recordings had been coded and mixed (by K.C.). Only beats with acceptable or good quality were used for measurements.

From M-mode echocardiographic recordings the measurements listed below were made on three beats (leading edge to leading edge method) according to the recommendations made by the American Society of Echocardiography[18], and the mean was used for further calculations. LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-diastole (the electrocardiographic Q wave), and at end-systole (the shortest distance between the septum and the posterior wall). M-mode echocardiographic dimensions and time intervals as well as amplitudes from pulse tracings were measured by means of a digitizing table-minicomputer system.

LV wall fractional thickening was calculated as septal and posterior wall systolic increase of thickness, respectively, divided by the corresponding diastolic thickness. Fractional shortening was defined as the difference between LV diastolic and systolic dimensions divided by the diastolic dimension. Ejection fraction was calculated according to the cube formula, for reasons discussed elsewhere[15]. Mean velocity of circumferential fibre shortening (mean Vcf) was calculated as fractional shortening divided by LV ejection time (LVET). Mean Vcf adjusted for heart rate (mean Vcf_c) was calculated as fractional shortening divided by LVET normalized by the square root of the cardiac cycle length in seconds[19]. Mitral E-point to septal separation (EPSS) was defined as the vertical distance (mean of five beats) between the E point of the anterior mitral leaflet and the ventricular septum[20,21]. EPSS was adjusted for end-diastolic LV dimension.

LV meridional end-systolic wall stress (ESWS) (10^3.dyn.cm^{-2}) was estimated as ESWS = (1·332 × pressure × D)/[4h × (1 + h/D)], where D represents LV end-systolic dimension and h stands for the mean of the septal and posterior wall end-systolic thickness[15,22]. Pressure was obtained by estimating end-systolic blood pressure from the carotid pulse tracing, where systolic and diastolic blood pressures were assigned to the peak and nadir of the carotid curve, respectively, and end-systolic blood pressure was estimated by linear interpolation to the height of the dicrotic notch[23]. End-systolic volume index (ESVI) was calculated as end-systolic volume/body surface area. As a measure of contractility, we also calculated the ratio ESWS/ESVI. The mean Vcf_c to be expected from the level of ESWS was calculated by means of the regression formula obtained from the relation between these two variables in the control group. The ratio between measured and expected mean Vcf_c was calculated as percentage (mean Vcf_c%).

From M-mode recordings, LV peak emptying rate as well as time from the electrocardiographic R-wave to peak emptying rate were measured by means of a digitizing table (Summagraphics ID-2CTR-TAB 17, Connecticut, U.S.A.) and a microcomputer (Professional-380, Digital Equipment Corp., U.S.A.), using an especially designed computer programme[15]. The same equipment was used for the evaluation of Doppler recordings. Measurements of aortic Doppler (pulsed and continuous) registrations were performed on five beats, and the mean value was used. Maximum LV emptying velocity was measured. Stroke volume was calculated as the velocity integral of pulsed Doppler systolic aortic flow, multiplied by the aortic area[24,25], where the latter was calculated at π(dimension/2)^2 from the aortic diameter (leading edge) just below the insertion of the aortic leaflets in parasternal 2-D echocardiographic projection.

Mean arterial pressure (MAP) was calculated according to the formula (systolic − diastolic blood pressure)/3 + diastolic blood pressure. Total peripheral resistance (TPR) was calculated according to the formula TPR = MAP × 1·33[60/Doppler cardiac output].

Measurements of pulse curve tracings were performed on five beats, and the mean values were used. The LVET, the electromechanical interval, the pre-ejection period (PEP) and the isovolumic contraction time (ICT), were measured as previously described, from the simultaneous recordings of the electrocardiographic lead II, the phonocardiogram and the carotid pulse tracing or apex-cardiogram[12]. Electromechanical interval and LVET were related to heart rate. LVET was therefore adjusted for heart according to the regression equation of the control group. The relative LVET was calculated as percentage of the expected normal LVET. PEP/LVET and ICT/LVET were calculated. Ratios in which LVET had been adjusted to heart rate 60 (LVET divided by square root of the cycle length in seconds) were also computed.

STATISTICAL ANALYSIS

Data are presented as mean ± standard error of the mean (SE). Unpaired two-sided t-test was used to compare differences between patients and controls. P values $< 0{\cdot}05$ were considered significant. For selected variables, abnormal values were defined by two standard deviations (SDs) of the control group.

Results

GENERAL CHARACTERISTICS

Clinical characteristics of the controls and the patients are shown in Table 1. In spite of similar heights, patients weighed less than controls as a group, and five patients had a low calculated body surface area. Blood pressure and TPR were similar in the two groups.

SYSTOLIC TIME INTERVALS

In the patient group, LVET was significantly shorter, and ICT as well as PEP were longer (Table 2). Also in the patient group, the ratios PEP/LVET and ICT/LVET were significantly higher, and differences remained when the LVET was adjusted for heart rate. Five patients had an increased PEP/LVET ratio.

ECHOCARDIOGRAPHY AND DOPPLER

When heart rate was measured during the echocardiographic investigation, patients had higher heart rates than controls (Table 3), but only one patient had a heart rate above the reference limit. Two patients had LV dilatation, but the mean values of end-diastolic and end-systolic LV internal dimensions did not differ between groups, nor did fractional shortening, mean Vcf or mean Vcf_c (Table 3). In spite of this, EPSS was larger in patients (increased in 26%). The difference regarding EPSS remained after adjustment for LV dimension. Septal fractioning thickening was reduced in systemic sclerosis, and stroke volume tended to be lower ($P = 0{\cdot}06$), as did stroke volume calculated from Doppler recordings (Table 4). ESWS was lower in the patient group (Table 3), and a difference remained when ESWS was adjusted for ESVI. Mean Vcf_c% tended to be lower in the patient group, and three patients had a reduced value. The peak rate of LV emptying, measured from M-mode echocardiography, was lower among patients (Table 3). The time from the

Table 2 Systolic time intervals

	Controls ($N=48$)	Patients ($N=30$)	P
LVET (ms)	323±4	303±6	0·007
PEP (ms)	96±3	110±5	0·01
ICT (ms)	40±3·2	51±4·2	0·04
PEP/LVET	0·30±0·01	0·37±0·02	0·0006
ICT/LVET	0·12±0·01	0·17±0·02	0·01
PEP/$LVET_c$	0·30±0·01	0·37±0·02	0·0006
ICT/$LVET_c$	0·12±0·01	0.17±0·02	0·01

Values are mean ±S.E. LVET=left ventricular ejection time; PEP=pre-ejection period; ICT=isovolumic contraction time; $LVET_c$=left ventricular time normalized for the square root of the cardiac cycle length.

Table 3 M-mode echocardiographic measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·6±1·4	67·5±1·7	0·01
LV dimension (Q) (mm)	49·9±0·8	48·5±1·4	N.S.
LV dimension (end-systole) (mm)	32·8±0·7	32·5±1·7	N.S.
Fractional thickening			
Septum (%)	43±3	30±4	0·007
Posterior wall (%)	61±4	53±5	N.S.
Stroke volume (ml)	94·5±4·9	80·4±5·0	N.S.
Ejection fraction	0·72±0·01	0·69±0·03	N.S.
Fractional shortening (%)	34·6±0·9	33·5±1·6	N.S.
Mean Vcf (circ s^{-1})	1·07±0·03	1·11±0·05	N.S.
Mean Vcf_c (circ s^{-1} $s^{0·5}$)	1·07±0·03	1·05±0·05	N.S.
Mean Vcf_c%	98·5±1·9	92·7±2·6	N.S.
ESWS (10^3.dyn.cm^{-2})	62·9±2·2	51·3±2·8	0·002
ESVI (ml m^{-2})	20·1±1·1	19·5±1·8	N.S.
ESWS/ESVI (10^3.dyn.cm^{-1}.ml^{-1}.cm^2)	3·34±0·13	2·9±0·16	0·03
EPSS (mm)	4·8±0·3	8·3±1·3	0·001
EPSS/LV dimension (Q)	0·098±0·01	0·162±0·02	0·0001
Peak emptying rate (mm s^{-2})	−105·5±4·2	−92·0±3·4	0·03
Time R wave to peak emptying rate (ms)	201·9±9·3	188·6±11·8	N.S.
Time to peak emptying (% of systole)	68·2±3·3	67·1±4·8	N.S.

Values are mean ±S.E. N.S. = not significant. LV=left ventricular; Vcf=velocity of circumferential fibre shortening; Vcf_c=Vcf adjusted for heart rate; Vcf_c%=measured/expected (from ESWS) Vcf_c; ESWS=end-systolic wall stress; ESVI=end-systolic volume index; EPSS=E-point septal separation.

R-wave to peak emptying did not differ, but, when calculated in relation to duration of systole, peak emptying occurred later in the patient group. When calculated from continuous wave Doppler (Table 4), the time to peak aortic flow acceleration, and also the time to peak aortic flow velocity, was longer in the patient group in spite of no significant difference regarding peak velocity of LV emptying (aortic flow acceleration) as calculated from Doppler.

INDIVIDUAL ABNORMALITIES

We evaluated the number of patients with abnormal values regarding the following variables: LV end-diastole dimension, ejection fraction, Vcf_c%, PEP/LVET, ICT/LVET, ESWS/ESVI, EPSS, time to peak aortic flow velocity and acceleration. Altogether, 18 patients (60%) had one or more abnormal findings regarding these variables. The variables displaying the highest prevalence of abnormal values were EPSS, time to peak flow velocity, PEP/LVET, and time to aortic peak flow acceleration. There was no significant relation between these variables and disease duration.

One patient had findings of dilated cardiomyopathy with a dilated left ventricle (77 mm) and a low ejection fraction (22%). Two other patients had low ejection fraction and low Vcf_c% in spite of LV dimension within the reference limits. Two patients had isolated abnormality of systolic time intervals and two patients isolated increase of EPSS.

Discussion

The present study is the first to compare LV function, in a consecutive series of patients with systemic sclerosis,

Table 4 Doppler measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·4±1·1	69·0±2·1	0·0008
Stroke volume (ml)	74·4±2·8	67·5±5·0	N.S.
Cardiac output (l min^{-1})	4·6±0·2	4·5±0·3	N.S.
Peak aortic gradient (mmHg)	5·3±0·4	5·0±0·5	N.S.
Time to peak velocity (% of systole)	25·0±0·8	31·7±1·6	0·0001
Peak acceleration (mmHg s^{-1})	111±6	104±11	N.S.
Time to peak acceleration (% of systole)	9·1±0·3	10·6±0·6	0·01

Values are mean ±S.E. N.S. = not significant.

with that of a random sample of matched control subjects from the general population. Great care was taken to ensure objective evaluation of data. Thus, the investigations were all carried out by the same investigator, who was unaware of the clinical findings. Interpretations were likewise performed by a single investigator, after blind-coding and mixing of the recordings from patients and controls.

Focal myocardial fibrosis reported by several authors[3,5,26], may be the reason for the development of myocardial dysfunction in systemic sclerosis. However, even patients with systemic sclerosis who died suddenly seem to display conspicuously normal extramural coronary arteries at autopsy[27,28]. Focal myocardial lesions have no relation to specific extramural vasculature[3], and myocardial necrosis occurs with widely patent intramural and extramural coronary arteries, suggesting the microcirculation is abnormal[28–30]. Although patients with arrhythmias and conduction disturbances who die suddenly have abnormalities of their sinus node artery and AV-node artery[27], an autopsy study of 52 patients have shown intramural coronary arteries to be generally normal histologically and microangiograms in 12 patients to be free from abnormalities[3]. Vasospasm or myocardial Raynaud's phenomenon have been suggested to be responsible for the myocardial necrosis seen in systemic sclerosis[28,29], and we were recently able to substantiate this hypothesis by showing in the present study group reversible myocardial perfusion defects induced by cold provocation[31]. Since in the patient with the largest myocardial perfusion defects arteriography showed normal coronary arteries, as did the angiograms from three randomly selected patients, we considered coronary arteriography to be neither necessary nor ethical in the remainder of the present study population. Moreover, we could not, for ethical reasons, have made comparative studies in the control group.

Some patients with systemic sclerosis develop severe cardiac involvement with a picture of dilated cardiomyopathy[32]. Such findings are, however, rare and were only seen in one patient in the present study, while two other patients had low ejection fraction without dilatation. Most patients had only a mild or moderate impairment of systolic function. Thus, the mean values of ejection fraction did not differ between the groups.

The systolic time intervals of the patients were clearly abnormal. One possible explanation for this is inclusion of patients with bundle branch block, while controls had normal transmission of depolarization potentials. Such an explanation was, however, not valid, since only one patient had right bundle branch block, and none had left bundle branch block. A more plausible explanation of abnormal systolic time intervals is obviously a true myocardial impairment.

The existence of myocardial dysfunction was substantiated by the findings of increased EPSS (with and without adjustment for LV dimension), reduced septal fractional thickening, reduced LV emptying by M-mode digitization, and delayed times to peak aortic flow acceleration and velocity by Doppler. The time for aortic flow to peak acceleration and velocity may be more sensitive indicators of contractility than peak acceleration, although also the latter tended to be abnormal.

We used EPSS in the present study since this measure has been shown to be a valid predictor of depressed systolic function independent of LV size and wall motion abnormalities, and better than other echocardiographic indices correlated to angiographic ejection fraction[20,33,34]. Mitral regurgitation causing a low afterload in the patient group is one possible explanation for the lack of difference between groups regarding fractional shortening and similar indices[35]. Although, Doppler evidence of mild mitral insufficiency was prevalent, moderate or severe regurgitation was rare (two patients) in systemic sclerosis (any degree of regurgitation found in 40% of patients vs 4% in the control group, $P<0·001$)[36], a low afterload being more probably explained by systolic impairment together with an increased relative wall thickness among patients[37]. The ratio ESWS/ESVI takes load into account, and a low value of this ratio indicates systolic impairment irrespective of mitral regurgitation[38]. Thus, the difference between groups regarding ESWS/ESVI means systolic impairment in the patient group.

We conclude that the systolic LV function in many patients with systemic sclerosis is impaired to a mild or moderate degree. The prevalence of more advanced involvement is low, possibly because of rapid deterioration in such cases. However, myocardial dysfunction seems to be detectable at an early stage when it could still be influenced by medical therapy. The cardiac effects of

treatment with angiotensin-converting-enzyme inhibitors is currently being evaluated in the present study population.

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References

[1] Medsger TA Jr. Systemic sclerosis (Scleroderma), eosinophilic fasciitis, and calcinosis. In: McCarthy DJ, Ed. Arthritis and allied conditions. A textbook of rheumatology. Philadelphia: Lea & Febiger, 1985, 994–1036.

[2] Weiss S, Stead EA, Warren JV, Bailey OT. Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma. Arch Intern Med 1943; 71: 749–76.

[3] Bulkley BH, Ridolfi RL, Slayer ER, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976; 53: 483–90.

[4] Mac Whorter JE, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). Am J Med 1974; 57: 566–75.

[5] Sackner MA, Heinz ER, Steinberg AJ. The heart in scleroderma. Am J Cardiol 1966; 17: 542–75.

[6] Gottdiener Moutsopoulos HM, Decker JL. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979; 66: 391–8.

[7] 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: 369–76.

[8] Orabona ML, Albino O. Systemic progressive sclerosis (or visceral scleroderma). Review of the literature and report of cases. Acta Med Scand 1958; 160 (Suppl): 160–70.

[9] Siegel RJ, O'Connor B, M Ena I, Criley JM. Left ventricular function at rest and during Raynaud's phenomenon in patients with scleroderma. Am Heart J 1984; 108: 1469–76.

[10] Gaffney FA, Anderson RJ, Nixon JV, Blomqvist CG, Moore Jr WE. Cardiovascular function in patients with progressive systemic sclerosis (scleroderma). Clin Cardiol 1982; 5: 569–76.

[11] Subcommittee for scleroderma criteria of American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581–90.

[12] Wikstrand J, Berglund G, Wilhelmsen L, Wallentin I. Value of systolic and diastolic time intervals. Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction. Br Heart J 1978; 40: 256–67.

[13] American Heart Association: Recommendation for human blood pressure. Determination by sphygmomanometer. Circulation 1980; 62: 1145A–55A.

[14] Caidahl K, Svärdsudd K, Eriksson H, Wilhelmsen L. Relation of dyspnea to left ventricular wall motion disturbances in a population of 67-year-old men. Am J Cardiol 1987; 59: 1277–82.

[15] Caidahl K, Eriksson H, Hartford M, Wikstrand J, Wallentin I, Svärdsudd K. Dyspnoea of cardiac origin in 67-year-old men: I. Relation to systolic left ventricular function and wall stress. The study of men born in 1913. Br Heart J 1988; 59: 319–28.

[16] Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiography determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425–31.

[17] Ihlen H, Pamile JP, Dale J *et al.* Determination of cardiac output by Doppler echocardiography. Br Heart J 1984; 51: 54–60.

[18] Sahn DJ, DeMaria A, Kisslo J, Weyman AI. The committee on M-mode standardization of the American Society of Echocardiology: Recommendation regarding quantitation in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation 1978; 58: 1072–8.

[19] Colan SD, Borow KM, Newmann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load independent index of myocardial contractility. J Am Coll Cardiol 1984; 4: 715–24.

[20] Lew W, Henning H, Schelbert H, Karliner JS. Assessment of mitral E point-septal separation as an index of left ventricular performance in patients with acute and previous myocardial infarction. Am J Cardiol 1978; 41: 836–45.

[21] Caidahl K, Svärdsudd K, Eriksson H *et al.* Dyspnea of cardiac origin in 67-year-old men: relation to clinical and non-invasive measures of cardiac function. Am J Noninv Cardiol 1988; 2: 59–68.

[22] Grossman W, Jones D, MacLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1987; 8: 384–94.

[23] Borow KM, Green LH, Grossman W, Branwald E. Left ventricular end-systolic stress shortening and stress-length relation in humans. Normal values and sensitivity inotropic state. Am J Cardiol 1982; 50: 1301–8.

[24] Hatle L, Angelsen B. Doppler ultrasound in cardiology: physical principles and clinical application. Second edition. Philadelphia: Lea & Febiger, 1986.

[25] Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. Pediatr Cardiol 1987; 8: 241–6.

[26] Leinwand I, Duryee AW, Richter MN. Scleroderma (based on a study of over 150 cases). Ann Intern Med 1954; 41: 1003–41.

[27] James TN. VIII. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974; 50: 844–56.

[28] Bulkley BH, Klacsmann PG, Hutchins GM. Angina pectoris, myocardial infarction and sudden cardiac death with normal coronary arteries: A clinicopathologic study of 9 patients with progressive systemic sclerosis. Am Heart J 1978; 95: 563–9.

[29] Follansbee WP, Curtiss EI, Medsger TA *et al.* Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N Engl J Med 1984; 310: 142–8.

[30] Kahan A, Nitenberg A, Foult JM *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985; 28: 637–45.

[31] Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. Lancet 1989; ii: 475–9.

[32] Eggebrecht RF, Kleiger RE. Echocardiographic pattern in scleroderma. Chest 1977; 71: 47–51.

[33] Child JS, Krivokapich J, Perloff JK. Effect of left ventricular size on mitral E point to ventricular septal separation in assessment of cardiac performance. Am Heart J 1981; 101: 797–804.

[34] Ahmadpour H, Shah AA, Allen JW *et al.* Mitral E point septal separation: a reliable index of left ventricular performance in coronary artery disease. Am Heart J 1983; 106: 21–8.

[35] Caidahl K, Larsson S, Südow G, Wallentin I, Angelhed J-E, Olsson SB. Conservative surgery for mitral valve prolapse with regurgitation: clinical follow-up and noninvasive assessment. Eur Heart J 1987; 8: 384–94.

[36] Kazzam E, Johansson C, Waldenström A, Hällgren R, Caidahl K. Doppler findings of mitral regurgitation and impaired left ventricular filling properties in systemic sclerosis. J Am Coll Cardiol 1990; 15 (Suppl): 273A (Abstr).

[37] Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in systemic sclerosis. J Int Med 1990; 228: 183–92.

[38] Carabello BA, Spann JF. The uses and limitations of end-systolic indexes of left ventricular function. Circulation 1984; 69: 1058–64.

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Non-invasive assessment of systolic left ventricular function in systemic sclerosis

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KEY WORDS: Doppler, echocardiography, left ventricle, systemic sclerosis, systolic function, time intervals, wall stress.

Systemic sclerosis is a multisystemic disorder, also affecting the heart. To evaluate its influence on systolic left ventricular (LV) function, we investigated 30 consecutive patients (age 54·5±2·4 years, 15 men and 15 women) and 48 controls matched for age and sex. All subjects were investigated by phonocardiography, pulse curve recordings, M-mode echocardiography, and by pulsed and continuous wave Doppler. Heart rate, blood pressure and peripheral resistance did not differ, but patients weighed less than controls (P<0·01). Systolic time intervals indicated systolic impairment, with an increased pre-ejection period to LV ejection time (LVET) ratio (0·37±0·02 vs 0·30±0·01 P<0·001), and also an increased isovolumic contraction time to LVET ratio (0·17±0·02 vs 0·12±0·01, P<0·02). The latter difference remained when LVET was adjusted for heart rate. Echocardiographic E-point to septal separation was increased in patients (8·3±1·3 vs 4·8±0·3 mm, P=0·001), also after adjustment for LV dimension (P=0·0001), while septal fractional thickening was decreased (P<0·01). End systolic wall stress (P=0·0002) and stress to volume ratio (P=0·03) were lower in systemic sclerosis. Peak LV emptying rate was also lower in the patient group when measured by echocardiography (P=0·03). There was no difference between groups regarding LV dimensions, fractional shortening or mean velocity of circumferential fibre shortening. While aortic Doppler peak emptying rate did not differ between groups, it occurred later in systole in the patient group (P<0·01) as did peak velocity (P=0·0001). Cardiac output did not differ between the groups. In all, 18 of 30 patients (60%) had a systolic abnormality. However, only one patient had dilated cardiomyopathy, and two other patients had poor systolic function without LV dilatation. There was no relation between disease duration and systolic LV function.

We conclude that, in a consecutive series of patients with systemic sclerosis, systolic LV function is frequently impaired. While time intervals, emptying rate, and wall fractional thickening are affected, cardiac output and LV cavity dimensions are usually not.

Introduction

Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin. Visceral involvement is also well recognized, particularly the lungs, heart, kidneys and the gastrointestinal tract[1]. Cardiac involvement has, since it was reported by Weiss *et al.* in 1943[2], been a subject of wide interest[3–6]. Involvement of the heart in systemic sclerosis is associated with poor prognosis[7–8]. Since myocardial impairment may escape clinical detection, it seems important to apply methods with the potential to reveal cardiac dysfunction. However, results from non-invasive studies of systolic function in systemic sclerosis are somewhat contradictory[9,10].

We therefore studied a series of 30 consecutive patients to evaluate the presence and extent of left ventricular (LV) systolic dysfunction in systemic sclerosis and related the results to those of matched controls.

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Subjects and methods

SUBJECTS

We studied 30 consecutive patients (15 men and 15 women) with systemic sclerosis according to the American Rheumatology Association (ARA) criteria[11]. The patients were referred from The Uppsala region to Uppsala University Hospital between December 1986 and March 1988. Their mean age was 54·5 (range 25–77) years, and their disease had been recognized for 5·6 (range 0·5–23) years. General characteristics are shown in Table 1. Three randomly selected patients, and the patient with the largest reversible perfusion defect shown by myocardial scintigraphy after cold provocation, were subjected to coronary arteriography, but none of the four patients demonstrated abnormal angiograms. One patient had right bundle branch block, while none was found to have left bundle branch block.

For comparative purposes, age- and sex-matched control subjects were selected from the general population of Uppsala. Every resident in Sweden has a national registration number that includes date of birth. The numbers are registered by the County Census Bureau in a population register, which includes vital statistics, and which by law must be kept up to date. A sample of 90 age- and

Table 1 Characteristics of controls and patients

	Controls ($N=48$)	Patients ($N=30$)	P
Age (years)	54·6±2·1	54·5±2·4	N.S.
Sex (female/male)	22/26	15/15	N.S.
Height (cm)	172·7±1·11	170·9±1·9	N.S.
Weight (kg)	72·6±1·7	65·1±2·0	0·01
Body surface area (m^2)	1·9±0·03	1·7±0·04	0·02
Body mass index ($kg\ m^{-2}$)	24·3±0·5	22·3±0·9	0·008
Systolic blood pressure (mmHg)	134·9±2·6	132·9±3·5	N.S.
Diastolic blood pressure (mmHg)	81·4±1·4	78·7±2·1	N.S.
Mean arterial blood pressure (mmHg)	99·3±1·5	96·8±2·1	N.S.
Total peripheral resistance ($dyn.s.cm^{-5}$)	1604±59	1723±132	N.S.

Values are mean ±S.E. N.S. = not significant.

sex-matched subjects (three for each patient) was drawn from the register. All 90 controls were informed about the investigation protocol, and 55 of them gave their consent to participate in the study. Controls were excluded if treated for hypertension, and if clinical history or electrocardiography revealed coronary or rheumatic heart disease. Controls were not excluded on the basis of blood pressure level. No control had bundle branch block. None had known renal or pulmonary disease. Of the 55 subjects willing to participate, two were excluded due to previous antihypertensive treatment, one due to an electrocardiogram (ECG) indicating coronary heart disease, one due to a clinical history suggestive of ischaemic heart disease, two subjects because of a history of rheumatic heart disease, and one subject because of inadequate recordings. The remaining 48 subjects (26 men and 22 females) had a mean age of 54·6 (range 25–77) years and were included as a healthy control group.

METHODS

A standard 12-lead resting ECG, pulse curves and phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as previously described[12]. In brief, simultaneous carotid pulse tracing, ECG (standard lead II) and a phonocardiogram from the third left parasternal intercostal space, were recorded at 100 mm s^{-1} at the end of normal relaxed expiration with the subject in the supine position. Apex-cardiographic registrations were obtained similarly, but with the patient lying in the left lateral position.

Blood pressure was recorded in the supine position after 30 min of rest, after pulse recordings and immediately before M-mode recordings. Standard sphygmomanometer technique was applied, and the mean of three readings was used. Systolic blood pressure was measured at phase one and diastolic blood pressure at the disappearance of Korotkoff sound-phase five[13].

Echocardiography was performed by means of a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2·5 or 3·5 MHz phased array transducer. Parasternal two-dimensional (2-D) echocardiographic views[14] were stored on VHS 0·5 inch video tapes by means of a Panasonic video recorder NV 8100. Two-D guided M-mode echocardiograms[15] were recorded on strip charts (Honeywell, 8100, dry Silver paper) at a speed of 50 mm.s^{-1}. These investigations were performed with the subject lying in the left lateral position.

To measure cardiac output[16,17], a Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record the aortic flow spectrum. A 2 MHz single crystal pulsed and continuous wave Doppler probe with a diameter of 13·7 mm was used. The examination was carried out with patients lying in the left lateral position using an apical approach. The area of the maximum LV apex pulsation was defined, and the transducer was placed slightly above, slightly below or directly over it. Both continous and pulsed wave Doppler spectrum were recorded, guided by the Doppler signal of valve closure and opening. The audible Doppler sound pattern from the blood flow was also used, and the transducer was manipulated until the best spectral display was obtained from the aortic flow. Strip chart recordings were obtained at a speed of 50 mm.s^{-1}.

MEASUREMENTS

All measuring points were agreed upon by two observers (E.K. and K.C.). One investigator (E.K.) carried out all interpretations after the recordings had been coded and mixed (by K.C.). Only beats with acceptable or good quality were used for measurements.

From M-mode echocardiographic recordings the measurements listed below were made on three beats (leading edge to leading edge method) according to the recommendations made by the American Society of Echocardiography[18], and the mean was used for further calculations. LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-diastole (the electrocardiographic Q wave), and at end-systole (the shortest distance between the septum and the posterior wall). M-mode echocardiographic dimensions and time intervals as well as amplitudes from pulse tracings were measured by means of a digitizing table-minicomputer system.

LV wall fractional thickening was calculated as septal and posterior wall systolic increase of thickness, respectively, divided by the corresponding diastolic thickness. Fractional shortening was defined as the difference between LV diastolic and systolic dimensions divided by the diastolic dimension. Ejection fraction was calculated according to the cube formula, for reasons discussed elsewhere[15]. Mean velocity of circumferential fibre shortening (mean Vcf) was calculated as fractional shortening divided by LV ejection time (LVET). Mean Vcf adjusted for heart rate (mean Vcf_c) was calculated as fractional shortening divided by LVET normalized by the square root of the cardiac cycle length in seconds[19]. Mitral E-point to septal separation (EPSS) was defined as the vertical distance (mean of five beats) between the E point of the anterior mitral leaflet and the ventricular septum[20,21]. EPSS was adjusted for end-diastolic LV dimension.

LV meridional end-systolic wall stress (ESWS) (10^3.dyn.cm^{-2}) was estimated as ESWS = (1·332 × pressure × D)/[4h × (1 + h/D)], where D represents LV end-systolic dimension and h stands for the mean of the septal and posterior wall end-systolic thickness[15,22]. Pressure was obtained by estimating end-systolic blood pressure from the carotid pulse tracing, where systolic and diastolic blood pressures were assigned to the peak and nadir of the carotid curve, respectively, and end-systolic blood pressure was estimated by linear interpolation to the height of the dicrotic notch[23]. End-systolic volume index (ESVI) was calculated as end-systolic volume/body surface area. As a measure of contractility, we also calculated the ratio ESWS/ESVI. The mean Vcf_c to be expected from the level of ESWS was calculated by means of the regression formula obtained from the relation between these two variables in the control group. The ratio between measured and expected mean Vcf_c was calculated as percentage (mean Vcf_c%).

From M-mode recordings, LV peak emptying rate as well as time from the electrocardiographic R-wave to peak emptying rate were measured by means of a digitizing table (Summagraphics ID-2CTR-TAB 17, Connecticut, U.S.A.) and a microcomputer (Professional-380, Digital Equipment Corp., U.S.A.), using an especially designed computer programme[15]. The same equipment was used for the evaluation of Doppler recordings. Measurements of aortic Doppler (pulsed and continuous) registrations were performed on five beats, and the mean value was used. Maximum LV emptying velocity was measured. Stroke volume was calculated as the velocity integral of pulsed Doppler systolic aortic flow, multiplied by the aortic area[24,25], where the latter was calculated at π(dimension/2)^2 from the aortic diameter (leading edge) just below the insertion of the aortic leaflets in parasternal 2-D echocardiographic projection.

Mean arterial pressure (MAP) was calculated according to the formula (systolic − diastolic blood pressure)/3 + diastolic blood pressure. Total peripheral resistance (TPR) was calculated according to the formula TPR = MAP × 1·33[60/Doppler cardiac output].

Measurements of pulse curve tracings were performed on five beats, and the mean values were used. The LVET, the electromechanical interval, the pre-ejection period (PEP) and the isovolumic contraction time (ICT), were measured as previously described, from the simultaneous recordings of the electrocardiographic lead II, the phonocardiogram and the carotid pulse tracing or apex-cardiogram[12]. Electromechanical interval and LVET were related to heart rate. LVET was therefore adjusted for heart according to the regression equation of the control group. The relative LVET was calculated as percentage of the expected normal LVET. PEP/LVET and ICT/LVET were calculated. Ratios in which LVET had been adjusted to heart rate 60 (LVET divided by square root of the cycle length in seconds) were also computed.

STATISTICAL ANALYSIS

Data are presented as mean ± standard error of the mean (SE). Unpaired two-sided t-test was used to compare differences between patients and controls. P values $< 0{\cdot}05$ were considered significant. For selected variables, abnormal values were defined by two standard deviations (SDs) of the control group.

Results

GENERAL CHARACTERISTICS

Clinical characteristics of the controls and the patients are shown in Table 1. In spite of similar heights, patients weighed less than controls as a group, and five patients had a low calculated body surface area. Blood pressure and TPR were similar in the two groups.

SYSTOLIC TIME INTERVALS

In the patient group, LVET was significantly shorter, and ICT as well as PEP were longer (Table 2). Also in the patient group, the ratios PEP/LVET and ICT/LVET were significantly higher, and differences remained when the LVET was adjusted for heart rate. Five patients had an increased PEP/LVET ratio.

ECHOCARDIOGRAPHY AND DOPPLER

When heart rate was measured during the echocardiographic investigation, patients had higher heart rates than controls (Table 3), but only one patient had a heart rate above the reference limit. Two patients had LV dilatation, but the mean values of end-diastolic and end-systolic LV internal dimensions did not differ between groups, nor did fractional shortening, mean Vcf or mean Vcf_c (Table 3). In spite of this, EPSS was larger in patients (increased in 26%). The difference regarding EPSS remained after adjustment for LV dimension. Septal fractioning thickening was reduced in systemic sclerosis, and stroke volume tended to be lower ($P = 0{\cdot}06$), as did stroke volume calculated from Doppler recordings (Table 4). ESWS was lower in the patient group (Table 3), and a difference remained when ESWS was adjusted for ESVI. Mean Vcf_c% tended to be lower in the patient group, and three patients had a reduced value. The peak rate of LV emptying, measured from M-mode echocardiography, was lower among patients (Table 3). The time from the

Table 2 Systolic time intervals

	Controls ($N=48$)	Patients ($N=30$)	P
LVET (ms)	323±4	303±6	0·007
PEP (ms)	96±3	110±5	0·01
ICT (ms)	40±3·2	51±4·2	0·04
PEP/LVET	0·30±0·01	0·37±0·02	0·0006
ICT/LVET	0·12±0·01	0·17±0·02	0·01
$PEP/LVET_c$	0·30±0·01	0·37±0·02	0·0006
$ICT/LVET_c$	0·12±0·01	0.17±0·02	0·01

Values are mean ±S.E. LVET=left ventricular ejection time; PEP=pre-ejection period; ICT=isovolumic contraction time; $LVET_c$=left ventricular time normalized for the square root of the cardiac cycle length.

Table 3 M-mode echocardiographic measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·6±1·4	67·5±1·7	0·01
LV dimension (Q) (mm)	49·9±0·8	48·5±1·4	N.S.
LV dimension (end-systole) (mm)	32·8±0·7	32·5±1·7	N.S.
Fractional thickening			
Septum (%)	43±3	30±4	0·007
Posterior wall (%)	61±4	53±5	N.S.
Stroke volume (ml)	94·5±4·9	80·4±5·0	N.S.
Ejection fraction	0·72±0·01	0·69±0·03	N.S.
Fractional shortening (%)	34·6±0·9	33·5±1·6	N.S.
Mean Vcf (circ s^{-1})	1·07±0·03	1·11±0·05	N.S.
Mean Vcf_c (circ s^{-1} $s^{0.5}$)	1·07±0·03	1·05±0·05	N.S.
Mean Vcf_c%	98·5±1·9	92·7±2·6	N.S.
ESWS (10^3.dyn.cm^{-2})	62·9±2·2	51·3±2·8	0·002
ESVI (ml m^{-2})	20·1±1·1	19·5±1·8	N.S.
ESWS/ESVI (10^3.dyn.cm^{-1}.ml^{-1}.cm^2)	3·34±0·13	2·9±0·16	0·03
EPSS (mm)	4·8±0·3	8·3±1·3	0·001
EPSS/LV dimension (Q)	0·098±0·01	0·162±0·02	0·0001
Peak emptying rate (mm s^{-2})	−105·5±4·2	−92·0±3·4	0·03
Time R wave to peak emptying rate (ms)	201·9±9·3	188·6±11·8	N.S.
Time to peak emptying (% of systole)	68·2±3·3	67·1±4·8	N.S.

Values are mean ±S.E. N.S. = not significant. LV=left ventricular; Vcf=velocity of circumferential fibre shortening; Vcf_c=Vcf adjusted for heart rate; Vcf_c%=measured/expected (from ESWS) Vcf_c; ESWS=end-systolic wall stress; ESVI=end-systolic volume index; EPSS=E-point septal separation.

R-wave to peak emptying did not differ, but, when calculated in relation to duration of systole, peak emptying occurred later in the patient group. When calculated from continuous wave Doppler (Table 4), the time to peak aortic flow acceleration, and also the time to peak aortic flow velocity, was longer in the patient group in spite of no significant difference regarding peak velocity of LV emptying (aortic flow acceleration) as calculated from Doppler.

INDIVIDUAL ABNORMALITIES

We evaluated the number of patients with abnormal values regarding the following variables: LV end-diastole dimension, ejection fraction, Vcf_c%, PEP/LVET, ICT/LVET, ESWS/ESVI, EPSS, time to peak aortic flow velocity and acceleration. Altogether, 18 patients (60%) had one or more abnormal findings regarding these variables. The variables displaying the highest prevalence of abnormal values were EPSS, time to peak flow velocity, PEP/LVET, and time to aortic peak flow acceleration. There was no significant relation between these variables and disease duration.

One patient had findings of dilated cardiomyopathy with a dilated left ventricle (77 mm) and a low ejection fraction (22%). Two other patients had low ejection fraction and low Vcf_c% in spite of LV dimension within the reference limits. Two patients had isolated abnormality of systolic time intervals and two patients isolated increase of EPSS.

Discussion

The present study is the first to compare LV function, in a consecutive series of patients with systemic sclerosis,

Table 4 Doppler measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·4±1·1	69·0±2·1	0·0008
Stroke volume (ml)	74·4±2·8	67·5±5·0	N.S.
Cardiac output (l min^{-1})	4·6±0·2	4·5±0·3	N.S.
Peak aortic gradient (mmHg)	5·3±0·4	5·0±0·5	N.S.
Time to peak velocity (% of systole)	25·0±0·8	31·7±1·6	0·0001
Peak acceleration (mmHg s^{-1})	111±6	104±11	N.S.
Time to peak acceleration (% of systole)	9·1±0·3	10·6±0·6	0·01

Values are mean ±S.E. N.S. = not significant.

with that of a random sample of matched control subjects from the general population. Great care was taken to ensure objective evaluation of data. Thus, the investigations were all carried out by the same investigator, who was unaware of the clinical findings. Interpretations were likewise performed by a single investigator, after blind-coding and mixing of the recordings from patients and controls.

Focal myocardial fibrosis reported by several authors[3,5,26], may be the reason for the development of myocardial dysfunction in systemic sclerosis. However, even patients with systemic sclerosis who died suddenly seem to display conspicuously normal extramural coronary arteries at autopsy[27,28]. Focal myocardial lesions have no relation to specific extramural vasculature[3], and myocardial necrosis occurs with widely patent intramural and extramural coronary arteries, suggesting the microcirculation is abnormal[28–30]. Although patients with arrhythmias and conduction disturbances who die suddenly have abnormalities of their sinus node artery and AV-node artery[27], an autopsy study of 52 patients have shown intramural coronary arteries to be generally normal histologically and microangiograms in 12 patients to be free from abnormalities[3]. Vasospasm or myocardial Raynaud's phenomenon have been suggested to be responsible for the myocardial necrosis seen in systemic sclerosis[28,29], and we were recently able to substantiate this hypothesis by showing in the present study group reversible myocardial perfusion defects induced by cold provocation[31]. Since in the patient with the largest myocardial perfusion defects arteriography showed normal coronary arteries, as did the angiograms from three randomly selected patients, we considered coronary arteriography to be neither necessary nor ethical in the remainder of the present study population. Moreover, we could not, for ethical reasons, have made comparative studies in the control group.

Some patients with systemic sclerosis develop severe cardiac involvement with a picture of dilated cardiomyopathy[32]. Such findings are, however, rare and were only seen in one patient in the present study, while two other patients had low ejection fraction without dilatation. Most patients had only a mild or moderate impairment of systolic function. Thus, the mean values of ejection fraction did not differ between the groups.

The systolic time intervals of the patients were clearly abnormal. One possible explanation for this is inclusion of patients with bundle branch block, while controls had normal transmission of depolarization potentials. Such an explanation was, however, not valid, since only one patient had right bundle branch block, and none had left bundle branch block. A more plausible explanation of abnormal systolic time intervals is obviously a true myocardial impairment.

The existence of myocardial dysfunction was substantiated by the findings of increased EPSS (with and without adjustment for LV dimension), reduced septal fractional thickening, reduced LV emptying by M-mode digitization, and delayed times to peak aortic flow acceleration and velocity by Doppler. The time for aortic flow to peak acceleration and velocity may be more sensitive indicators of contractility than peak acceleration, although also the latter tended to be abnormal.

We used EPSS in the present study since this measure has been shown to be a valid predictor of depressed systolic function independent of LV size and wall motion abnormalities, and better than other echocardiographic indices correlated to angiographic ejection fraction[20,33,34]. Mitral regurgitation causing a low afterload in the patient group is one possible explanation for the lack of difference between groups regarding fractional shortening and similar indices[35]. Although, Doppler evidence of mild mitral insufficiency was prevalent, moderate or severe regurgitation was rare (two patients) in systemic sclerosis (any degree of regurgitation found in 40% of patients vs 4% in the control group, $P<0·001$)[36], a low afterload being more probably explained by systolic impairment together with an increased relative wall thickness among patients[37]. The ratio ESWS/ESVI takes load into account, and a low value of this ratio indicates systolic impairment irrespective of mitral regurgitation[38]. Thus, the difference between groups regarding ESWS/ESVI means systolic impairment in the patient group.

We conclude that the systolic LV function in many patients with systemic sclerosis is impaired to a mild or moderate degree. The prevalence of more advanced involvement is low, possibly because of rapid deterioration in such cases. However, myocardial dysfunction seems to be detectable at an early stage when it could still be influenced by medical therapy. The cardiac effects of

treatment with angiotensin-converting-enzyme inhibitors is currently being evaluated in the present study population.

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References

[1] Medsger TA Jr. Systemic sclerosis (Scleroderma), eosinophilic fasciitis, and calcinosis. In: McCarthy DJ, Ed. Arthritis and allied conditions. A textbook of rheumatology. Philadelphia: Lea & Febiger, 1985, 994–1036.

[2] Weiss S, Stead EA, Warren JV, Bailey OT. Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma. Arch Intern Med 1943; 71: 749–76.

[3] Bulkley BH, Ridolfi RL, Slayer ER, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976; 53: 483–90.

[4] Mac Whorter JE, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). Am J Med 1974; 57: 566–75.

[5] Sackner MA, Heinz ER, Steinberg AJ. The heart in scleroderma. Am J Cardiol 1966; 17: 542–75.

[6] Gottdiener Moutsopoulos HM, Decker JL. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979; 66: 391–8.

[7] 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: 369–76.

[8] Orabona ML, Albino O. Systemic progressive sclerosis (or visceral scleroderma). Review of the literature and report of cases. Acta Med Scand 1958; 160 (Suppl): 160–70.

[9] Siegel RJ, O'Connor B, M Ena I, Criley JM. Left ventricular function at rest and during Raynaud's phenomenon in patients with scleroderma. Am Heart J 1984; 108: 1469–76.

[10] Gaffney FA, Anderson RJ, Nixon JV, Blomqvist CG, Moore Jr WE. Cardiovascular function in patients with progressive systemic sclerosis (scleroderma). Clin Cardiol 1982; 5: 569–76.

[11] Subcommittee for scleroderma criteria of American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581–90.

[12] Wikstrand J, Berglund G, Wilhelmsen L, Wallentin I. Value of systolic and diastolic time intervals. Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction. Br Heart J 1978; 40: 256–67.

[13] American Heart Association: Recommendation for human blood pressure. Determination by sphygmomanometer. Circulation 1980; 62: 1145A–55A.

[14] Caidahl K, Svärdsudd K, Eriksson H, Wilhelmsen L. Relation of dyspnea to left ventricular wall motion disturbances in a population of 67-year-old men. Am J Cardiol 1987; 59: 1277–82.

[15] Caidahl K, Eriksson H, Hartford M, Wikstrand J, Wallentin I, Svärdsudd K. Dyspnoea of cardiac origin in 67-year-old men: I. Relation to systolic left ventricular function and wall stress. The study of men born in 1913. Br Heart J 1988; 59: 319–28.

[16] Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiography determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425–31.

[17] Ihlen H, Pamile JP, Dale J *et al.* Determination of cardiac output by Doppler echocardiography. Br Heart J 1984; 51: 54–60.

[18] Sahn DJ, DeMaria A, Kisslo J, Weyman AI. The committee on M-mode standardization of the American Society of Echocardiology: Recommendation regarding quantitation in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation 1978; 58: 1072–8.

[19] Colan SD, Borow KM, Newmann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load independent index of myocardial contractility. J Am Coll Cardiol 1984; 4: 715–24.

[20] Lew W, Henning H, Schelbert H, Karliner JS. Assessment of mitral E point-septal separation as an index of left ventricular performance in patients with acute and previous myocardial infarction. Am J Cardiol 1978; 41: 836–45.

[21] Caidahl K, Svärdsudd K, Eriksson H *et al.* Dyspnea of cardiac origin in 67-year-old men: relation to clinical and non-invasive measures of cardiac function. Am J Noninv Cardiol 1988; 2: 59–68.

[22] Grossman W, Jones D, MacLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1987; 8: 384–94.

[23] Borow KM, Green LH, Grossman W, Branwald E. Left ventricular end-systolic stress shortening and stress-length relation in humans. Normal values and sensitivity inotropic state. Am J Cardiol 1982; 50: 1301–8.

[24] Hatle L, Angelsen B. Doppler ultrasound in cardiology: physical principles and clinical application. Second edition. Philadelphia: Lea & Febiger, 1986.

[25] Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. Pediatr Cardiol 1987; 8: 241–6.

[26] Leinwand I, Duryee AW, Richter MN. Scleroderma (based on a study of over 150 cases). Ann Intern Med 1954; 41: 1003–41.

[27] James TN. VIII. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974; 50: 844–56.

[28] Bulkley BH, Klacsmann PG, Hutchins GM. Angina pectoris, myocardial infarction and sudden cardiac death with normal coronary arteries: A clinicopathologic study of 9 patients with progressive systemic sclerosis. Am Heart J 1978; 95: 563–9.

[29] Follansbee WP, Curtiss EI, Medsger TA *et al.* Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N Engl J Med 1984; 310: 142–8.

[30] Kahan A, Nitenberg A, Foult JM *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985; 28: 637–45.

[31] Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. Lancet 1989; ii: 475–9.

[32] Eggebrecht RF, Kleiger RE. Echocardiographic pattern in scleroderma. Chest 1977; 71: 47–51.

[33] Child JS, Krivokapich J, Perloff JK. Effect of left ventricular size on mitral E point to ventricular septal separation in assessment of cardiac performance. Am Heart J 1981; 101: 797–804.

[34] Ahmadpour H, Shah AA, Allen JW *et al.* Mitral E point septal separation: a reliable index of left ventricular performance in coronary artery disease. Am Heart J 1983; 106: 21–8.

[35] Caidahl K, Larsson S, Südow G, Wallentin I, Angelhed J-E, Olsson SB. Conservative surgery for mitral valve prolapse with regurgitation: clinical follow-up and noninvasive assessment. Eur Heart J 1987; 8: 384–94.

[36] Kazzam E, Johansson C, Waldenström A, Hällgren R, Caidahl K. Doppler findings of mitral regurgitation and impaired left ventricular filling properties in systemic sclerosis. J Am Coll Cardiol 1990; 15 (Suppl): 273A (Abstr).

[37] Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in systemic sclerosis. J Int Med 1990; 228: 183–92.

[38] Carabello BA, Spann JF. The uses and limitations of end-systolic indexes of left ventricular function. Circulation 1984; 69: 1058–64.

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Non-invasive assessment of systolic left ventricular function in systemic sclerosis

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KEY WORDS: Doppler, echocardiography, left ventricle, systemic sclerosis, systolic function, time intervals, wall stress.

Systemic sclerosis is a multisystemic disorder, also affecting the heart. To evaluate its influence on systolic left ventricular (LV) function, we investigated 30 consecutive patients (age 54·5±2·4 years, 15 men and 15 women) and 48 controls matched for age and sex. All subjects were investigated by phonocardiography, pulse curve recordings, M-mode echocardiography, and by pulsed and continuous wave Doppler. Heart rate, blood pressure and peripheral resistance did not differ, but patients weighed less than controls (P<0·01). Systolic time intervals indicated systolic impairment, with an increased pre-ejection period to LV ejection time (LVET) ratio (0·37±0·02 vs 0·30±0·01 P<0·001), and also an increased isovolumic contraction time to LVET ratio (0·17±0·02 vs 0·12±0·01, P<0·02). The latter difference remained when LVET was adjusted for heart rate. Echocardiographic E-point to septal separation was increased in patients (8·3±1·3 vs 4·8±0·3 mm, P=0·001), also after adjustment for LV dimension (P=0·0001), while septal fractional thickening was decreased (P<0·01). End systolic wall stress (P=0·0002) and stress to volume ratio (P=0·03) were lower in systemic sclerosis. Peak LV emptying rate was also lower in the patient group when measured by echocardiography (P=0·03). There was no difference between groups regarding LV dimensions, fractional shortening or mean velocity of circumferential fibre shortening. While aortic Doppler peak emptying rate did not differ between groups, it occurred later in systole in the patient group (P<0·01) as did peak velocity (P=0·0001). Cardiac output did not differ between the groups. In all, 18 of 30 patients (60%) had a systolic abnormality. However, only one patient had dilated cardiomyopathy, and two other patients had poor systolic function without LV dilatation. There was no relation between disease duration and systolic LV function.

We conclude that, in a consecutive series of patients with systemic sclerosis, systolic LV function is frequently impaired. While time intervals, emptying rate, and wall fractional thickening are affected, cardiac output and LV cavity dimensions are usually not.

Introduction

Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin. Visceral involvement is also well recognized, particularly the lungs, heart, kidneys and the gastrointestinal tract[1]. Cardiac involvement has, since it was reported by Weiss *et al.* in 1943[2], been a subject of wide interest[3–6]. Involvement of the heart in systemic sclerosis is associated with poor prognosis[7–8]. Since myocardial impairment may escape clinical detection, it seems important to apply methods with the potential to reveal cardiac dysfunction. However, results from non-invasive studies of systolic function in systemic sclerosis are somewhat contradictory[9,10].

We therefore studied a series of 30 consecutive patients to evaluate the presence and extent of left ventricular (LV) systolic dysfunction in systemic sclerosis and related the results to those of matched controls.

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Subjects and methods

SUBJECTS

We studied 30 consecutive patients (15 men and 15 women) with systemic sclerosis according to the American Rheumatology Association (ARA) criteria[11]. The patients were referred from The Uppsala region to Uppsala University Hospital between December 1986 and March 1988. Their mean age was 54·5 (range 25–77) years, and their disease had been recognized for 5·6 (range 0·5–23) years. General characteristics are shown in Table 1. Three randomly selected patients, and the patient with the largest reversible perfusion defect shown by myocardial scintigraphy after cold provocation, were subjected to coronary arteriography, but none of the four patients demonstrated abnormal angiograms. One patient had right bundle branch block, while none was found to have left bundle branch block.

For comparative purposes, age- and sex-matched control subjects were selected from the general population of Uppsala. Every resident in Sweden has a national registration number that includes date of birth. The numbers are registered by the County Census Bureau in a population register, which includes vital statistics, and which by law must be kept up to date. A sample of 90 age- and

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Table 1 Characteristics of controls and patients

	Controls ($N=48$)	Patients ($N=30$)	P
Age (years)	54·6±2·1	54·5±2·4	N.S.
Sex (female/male)	22/26	15/15	N.S.
Height (cm)	172·7±1·11	170·9±1·9	N.S.
Weight (kg)	72·6±1·7	65·1±2·0	0·01
Body surface area (m^2)	1·9±0·03	1·7±0·04	0·02
Body mass index ($kg\ m^{-2}$)	24·3±0·5	22·3±0·9	0·008
Systolic blood pressure (mmHg)	134·9±2·6	132·9±3·5	N.S.
Diastolic blood pressure (mmHg)	81·4±1·4	78·7±2·1	N.S.
Mean arterial blood pressure (mmHg)	99·3±1·5	96·8±2·1	N.S.
Total peripheral resistance ($dyn.s.cm^{-5}$)	1604±59	1723±132	N.S.

Values are mean ±S.E. N.S. = not significant.

sex-matched subjects (three for each patient) was drawn from the register. All 90 controls were informed about the investigation protocol, and 55 of them gave their consent to participate in the study. Controls were excluded if treated for hypertension, and if clinical history or electrocardiography revealed coronary or rheumatic heart disease. Controls were not excluded on the basis of blood pressure level. No control had bundle branch block. None had known renal or pulmonary disease. Of the 55 subjects willing to participate, two were excluded due to previous antihypertensive treatment, one due to an electrocardiogram (ECG) indicating coronary heart disease, one due to a clinical history suggestive of ischaemic heart disease, two subjects because of a history of rheumatic heart disease, and one subject because of inadequate recordings. The remaining 48 subjects (26 men and 22 females) had a mean age of 54·6 (range 25–77) years and were included as a healthy control group.

METHODS

A standard 12-lead resting ECG, pulse curves and phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as previously described[12]. In brief, simultaneous carotid pulse tracing, ECG (standard lead II) and a phonocardiogram from the third left parasternal intercostal space, were recorded at 100 mm s^{-1} at the end of normal relaxed expiration with the subject in the supine position. Apex-cardiographic registrations were obtained similarly, but with the patient lying in the left lateral position.

Blood pressure was recorded in the supine position after 30 min of rest, after pulse recordings and immediately before M-mode recordings. Standard sphygmomanometer technique was applied, and the mean of three readings was used. Systolic blood pressure was measured at phase one and diastolic blood pressure at the disappearance of Korotkoff sound-phase five[13].

Echocardiography was performed by means of a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2·5 or 3·5 MHz phased array transducer. Parasternal two-dimensional (2-D) echocardiographic views[14] were stored on VHS 0·5 inch video tapes by means of a Panasonic video recorder NV 8100. Two-D guided M-mode echocardiograms[15] were recorded on strip charts (Honeywell, 8100, dry Silver paper) at a speed of 50 mm.s^{-1}. These investigations were performed with the subject lying in the left lateral position.

To measure cardiac output[16,17], a Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record the aortic flow spectrum. A 2 MHz single crystal pulsed and continuous wave Doppler probe with a diameter of 13·7 mm was used. The examination was carried out with patients lying in the left lateral position using an apical approach. The area of the maximum LV apex pulsation was defined, and the transducer was placed slightly above, slightly below or directly over it. Both continous and pulsed wave Doppler spectrum were recorded, guided by the Doppler signal of valve closure and opening. The audible Doppler sound pattern from the blood flow was also used, and the transducer was manipulated until the best spectral display was obtained from the aortic flow. Strip chart recordings were obtained at a speed of 50 mm.s^{-1}.

MEASUREMENTS

All measuring points were agreed upon by two observers (E.K. and K.C.). One investigator (E.K.) carried out all interpretations after the recordings had been coded and mixed (by K.C.). Only beats with acceptable or good quality were used for measurements.

From M-mode echocardiographic recordings the measurements listed below were made on three beats (leading edge to leading edge method) according to the recommendations made by the American Society of Echocardiography[18], and the mean was used for further calculations. LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-diastole (the electrocardiographic Q wave), and at end-systole (the shortest distance between the septum and the posterior wall). M-mode echocardiographic dimensions and time intervals as well as amplitudes from pulse tracings were measured by means of a digitizing table-minicomputer system.

LV wall fractional thickening was calculated as septal and posterior wall systolic increase of thickness, respectively, divided by the corresponding diastolic thickness. Fractional shortening was defined as the difference between LV diastolic and systolic dimensions divided by the diastolic dimension. Ejection fraction was calculated according to the cube formula, for reasons discussed elsewhere[15]. Mean velocity of circumferential fibre shortening (mean Vcf) was calculated as fractional shortening divided by LV ejection time (LVET). Mean Vcf adjusted for heart rate (mean Vcf_c) was calculated as fractional shortening divided by LVET normalized by the square root of the cardiac cycle length in seconds[19]. Mitral E-point to septal separation (EPSS) was defined as the vertical distance (mean of five beats) between the E point of the anterior mitral leaflet and the ventricular septum[20,21]. EPSS was adjusted for end-diastolic LV dimension.

LV meridional end-systolic wall stress (ESWS) (10^3.dyn.cm^{-2}) was estimated as ESWS = (1·332 × pressure × D)/[4h × (1 + h/D)], where D represents LV end-systolic dimension and h stands for the mean of the septal and posterior wall end-systolic thickness[15,22]. Pressure was obtained by estimating end-systolic blood pressure from the carotid pulse tracing, where systolic and diastolic blood pressures were assigned to the peak and nadir of the carotid curve, respectively, and end-systolic blood pressure was estimated by linear interpolation to the height of the dicrotic notch[23]. End-systolic volume index (ESVI) was calculated as end-systolic volume/body surface area. As a measure of contractility, we also calculated the ratio ESWS/ESVI. The mean Vcf_c to be expected from the level of ESWS was calculated by means of the regression formula obtained from the relation between these two variables in the control group. The ratio between measured and expected mean Vcf_c was calculated as percentage (mean Vcf_c%).

From M-mode recordings, LV peak emptying rate as well as time from the electrocardiographic R-wave to peak emptying rate were measured by means of a digitizing table (Summagraphics ID-2CTR-TAB 17, Connecticut, U.S.A.) and a microcomputer (Professional-380, Digital Equipment Corp., U.S.A.), using an especially designed computer programme[15]. The same equipment was used for the evaluation of Doppler recordings. Measurements of aortic Doppler (pulsed and continuous) registrations were performed on five beats, and the mean value was used. Maximum LV emptying velocity was measured. Stroke volume was calculated as the velocity integral of pulsed Doppler systolic aortic flow, multiplied by the aortic area[24,25], where the latter was calculated at π(dimension/2)^2 from the aortic diameter (leading edge) just below the insertion of the aortic leaflets in parasternal 2-D echocardiographic projection.

Mean arterial pressure (MAP) was calculated according to the formula (systolic − diastolic blood pressure)/3 + diastolic blood pressure. Total peripheral resistance (TPR) was calculated according to the formula TPR = MAP × 1·33[60/Doppler cardiac output].

Measurements of pulse curve tracings were performed on five beats, and the mean values were used. The LVET, the electromechanical interval, the pre-ejection period (PEP) and the isovolumic contraction time (ICT), were measured as previously described, from the simultaneous recordings of the electrocardiographic lead II, the phonocardiogram and the carotid pulse tracing or apex-cardiogram[12]. Electromechanical interval and LVET were related to heart rate. LVET was therefore adjusted for heart according to the regression equation of the control group. The relative LVET was calculated as percentage of the expected normal LVET. PEP/LVET and ICT/LVET were calculated. Ratios in which LVET had been adjusted to heart rate 60 (LVET divided by square root of the cycle length in seconds) were also computed.

STATISTICAL ANALYSIS

Data are presented as mean ± standard error of the mean (SE). Unpaired two-sided t-test was used to compare differences between patients and controls. *P* values $<0·05$ were considered significant. For selected variables, abnormal values were defined by two standard deviations (SDs) of the control group.

Results

GENERAL CHARACTERISTICS

Clinical characteristics of the controls and the patients are shown in Table 1. In spite of similar heights, patients weighed less than controls as a group, and five patients had a low calculated body surface area. Blood pressure and TPR were similar in the two groups.

SYSTOLIC TIME INTERVALS

In the patient group, LVET was significantly shorter, and ICT as well as PEP were longer (Table 2). Also in the patient group, the ratios PEP/LVET and ICT/LVET were significantly higher, and differences remained when the LVET was adjusted for heart rate. Five patients had an increased PEP/LVET ratio.

ECHOCARDIOGRAPHY AND DOPPLER

When heart rate was measured during the echocardiographic investigation, patients had higher heart rates than controls (Table 3), but only one patient had a heart rate above the reference limit. Two patients had LV dilatation, but the mean values of end-diastolic and end-systolic LV internal dimensions did not differ between groups, nor did fractional shortening, mean Vcf or mean Vcf_c (Table 3). In spite of this, EPSS was larger in patients (increased in 26%). The difference regarding EPSS remained after adjustment for LV dimension. Septal fractioning thickening was reduced in systemic sclerosis, and stroke volume tended to be lower ($P = 0·06$), as did stroke volume calculated from Doppler recordings (Table 4). ESWS was lower in the patient group (Table 3), and a difference remained when ESWS was adjusted for ESVI. Mean Vcf_c% tended to be lower in the patient group, and three patients had a reduced value. The peak rate of LV emptying, measured from M-mode echocardiography, was lower among patients (Table 3). The time from the

Table 2 Systolic time intervals

	Controls ($N=48$)	Patients ($N=30$)	P
LVET (ms)	323±4	303±6	0·007
PEP (ms)	96±3	110±5	0·01
ICT (ms)	40±3·2	51±4·2	0·04
PEP/LVET	0·30±0·01	0·37±0·02	0·0006
ICT/LVET	0·12±0·01	0·17±0·02	0·01
$PEP/LVET_c$	0·30±0·01	0·37±0·02	0·0006
$ICT/LVET_c$	0·12±0·01	0.17±0·02	0·01

Values are mean ±S.E. LVET=left ventricular ejection time; PEP=pre-ejection period; ICT=isovolumic contraction time; $LVET_c$=left ventricular time normalized for the square root of the cardiac cycle length.

Table 3 M-mode echocardiographic measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·6±1·4	67·5±1·7	0·01
LV dimension (Q) (mm)	49·9±0·8	48·5±1·4	N.S.
LV dimension (end-systole) (mm)	32·8±0·7	32·5±1·7	N.S.
Fractional thickening			
Septum (%)	43±3	30±4	0·007
Posterior wall (%)	61±4	53±5	N.S.
Stroke volume (ml)	94·5±4·9	80·4±5·0	N.S.
Ejection fraction	0·72±0·01	0·69±0·03	N.S.
Fractional shortening (%)	34·6±0·9	33·5±1·6	N.S.
Mean Vcf (circ s^{-1})	1·07±0·03	1·11±0·05	N.S.
Mean Vcf_c (circ s^{-1} $s^{0·5}$)	1·07±0·03	1·05±0·05	N.S.
Mean Vcf_c%	98·5±1·9	92·7±2·6	N.S.
ESWS (10^3.dyn.cm^{-2})	62·9±2·2	51·3±2·8	0·002
ESVI (ml m^{-2})	20·1±1·1	19·5±1·8	N.S.
ESWS/ESVI (10^3.dyn.cm^{-1}.ml^{-1}.cm^2)	3·34±0·13	2·9±0·16	0·03
EPSS (mm)	4·8±0·3	8·3±1·3	0·001
EPSS/LV dimension (Q)	0·098±0·01	0·162±0·02	0·0001
Peak emptying rate (mm s^{-2})	−105·5±4·2	−92·0±3·4	0·03
Time R wave to peak emptying rate (ms)	201·9±9·3	188·6±11·8	N.S.
Time to peak emptying (% of systole)	68·2±3·3	67·1±4·8	N.S.

Values are mean ±S.E. N.S. = not significant. LV=left ventricular; Vcf=velocity of circumferential fibre shortening; Vcf_c=Vcf adjusted for heart rate; Vcf_c%=measured/expected (from ESWS) Vcf_c; ESWS=end-systolic wall stress; ESVI=end-systolic volume index; EPSS=E-point septal separation.

R-wave to peak emptying did not differ, but, when calculated in relation to duration of systole, peak emptying occurred later in the patient group. When calculated from continuous wave Doppler (Table 4), the time to peak aortic flow acceleration, and also the time to peak aortic flow velocity, was longer in the patient group in spite of no significant difference regarding peak velocity of LV emptying (aortic flow acceleration) as calculated from Doppler.

INDIVIDUAL ABNORMALITIES

We evaluated the number of patients with abnormal values regarding the following variables: LV end-diastole dimension, ejection fraction, Vcf_c%, PEP/LVET, ICT/LVET, ESWS/ESVI, EPSS, time to peak aortic flow velocity and acceleration. Altogether, 18 patients (60%) had one or more abnormal findings regarding these variables. The variables displaying the highest prevalence of abnormal values were EPSS, time to peak flow velocity, PEP/LVET, and time to aortic peak flow acceleration. There was no significant relation between these variables and disease duration.

One patient had findings of dilated cardiomyopathy with a dilated left ventricle (77 mm) and a low ejection fraction (22%). Two other patients had low ejection fraction and low Vcf_c% in spite of LV dimension within the reference limits. Two patients had isolated abnormality of systolic time intervals and two patients isolated increase of EPSS.

Discussion

The present study is the first to compare LV function, in a consecutive series of patients with systemic sclerosis,

Table 4 Doppler measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·4±1·1	69·0±2·1	0·0008
Stroke volume (ml)	74·4±2·8	67·5±5·0	N.S.
Cardiac output (l min^{-1})	4·6±0·2	4·5±0·3	N.S.
Peak aortic gradient (mmHg)	5·3±0·4	5·0±0·5	N.S.
Time to peak velocity (% of systole)	25·0±0·8	31·7±1·6	0·0001
Peak acceleration (mmHg s^{-1})	111±6	104±11	N.S.
Time to peak acceleration (% of systole)	9·1±0·3	10·6±0·6	0·01

Values are mean ±S.E. N.S. = not significant.

with that of a random sample of matched control subjects from the general population. Great care was taken to ensure objective evaluation of data. Thus, the investigations were all carried out by the same investigator, who was unaware of the clinical findings. Interpretations were likewise performed by a single investigator, after blind-coding and mixing of the recordings from patients and controls.

Focal myocardial fibrosis reported by several authors[3,5,26], may be the reason for the development of myocardial dysfunction in systemic sclerosis. However, even patients with systemic sclerosis who died suddenly seem to display conspicuously normal extramural coronary arteries at autopsy[27,28]. Focal myocardial lesions have no relation to specific extramural vasculature[3], and myocardial necrosis occurs with widely patent intramural and extramural coronary arteries, suggesting the microcirculation is abnormal[28–30]. Although patients with arrhythmias and conduction disturbances who die suddenly have abnormalities of their sinus node artery and AV-node artery[27], an autopsy study of 52 patients have shown intramural coronary arteries to be generally normal histologically and microangiograms in 12 patients to be free from abnormalities[3]. Vasospasm or myocardial Raynaud's phenomenon have been suggested to be responsible for the myocardial necrosis seen in systemic sclerosis[28,29], and we were recently able to substantiate this hypothesis by showing in the present study group reversible myocardial perfusion defects induced by cold provocation[31]. Since in the patient with the largest myocardial perfusion defects arteriography showed normal coronary arteries, as did the angiograms from three randomly selected patients, we considered coronary arteriography to be neither necessary nor ethical in the remainder of the present study population. Moreover, we could not, for ethical reasons, have made comparative studies in the control group.

Some patients with systemic sclerosis develop severe cardiac involvement with a picture of dilated cardiomyopathy[32]. Such findings are, however, rare and were only seen in one patient in the present study, while two other patients had low ejection fraction without dilatation. Most patients had only a mild or moderate impairment of systolic function. Thus, the mean values of ejection fraction did not differ between the groups.

The systolic time intervals of the patients were clearly abnormal. One possible explanation for this is inclusion of patients with bundle branch block, while controls had normal transmission of depolarization potentials. Such an explanation was, however, not valid, since only one patient had right bundle branch block, and none had left bundle branch block. A more plausible explanation of abnormal systolic time intervals is obviously a true myocardial impairment.

The existence of myocardial dysfunction was substantiated by the findings of increased EPSS (with and without adjustment for LV dimension), reduced septal fractional thickening, reduced LV emptying by M-mode digitization, and delayed times to peak aortic flow acceleration and velocity by Doppler. The time for aortic flow to peak acceleration and velocity may be more sensitive indicators of contractility than peak acceleration, although also the latter tended to be abnormal.

We used EPSS in the present study since this measure has been shown to be a valid predictor of depressed systolic function independent of LV size and wall motion abnormalities, and better than other echocardiographic indices correlated to angiographic ejection fraction[20,33,34]. Mitral regurgitation causing a low afterload in the patient group is one possible explanation for the lack of difference between groups regarding fractional shortening and similar indices[35]. Although, Doppler evidence of mild mitral insufficiency was prevalent, moderate or severe regurgitation was rare (two patients) in systemic sclerosis (any degree of regurgitation found in 40% of patients vs 4% in the control group, $P<0·001$)[36], a low afterload being more probably explained by systolic impairment together with an increased relative wall thickness among patients[37]. The ratio ESWS/ESVI takes load into account, and a low value of this ratio indicates systolic impairment irrespective of mitral regurgitation[38]. Thus, the difference between groups regarding ESWS/ESVI means systolic impairment in the patient group.

We conclude that the systolic LV function in many patients with systemic sclerosis is impaired to a mild or moderate degree. The prevalence of more advanced involvement is low, possibly because of rapid deterioration in such cases. However, myocardial dysfunction seems to be detectable at an early stage when it could still be influenced by medical therapy. The cardiac effects of

treatment with angiotensin-converting-enzyme inhibitors is currently being evaluated in the present study population.

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References

[1] Medsger TA Jr. Systemic sclerosis (Scleroderma), eosinophilic fasciitis, and calcinosis. In: McCarthy DJ, Ed. Arthritis and allied conditions. A textbook of rheumatology. Philadelphia: Lea & Febiger, 1985, 994–1036.

[2] Weiss S, Stead EA, Warren JV, Bailey OT. Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma. Arch Intern Med 1943; 71: 749–76.

[3] Bulkley BH, Ridolfi RL, Slayer ER, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976; 53: 483–90.

[4] Mac Whorter JE, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). Am J Med 1974; 57: 566–75.

[5] Sackner MA, Heinz ER, Steinberg AJ. The heart in scleroderma. Am J Cardiol 1966; 17: 542–75.

[6] Gottdiener Moutsopoulos HM, Decker JL. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979; 66: 391–8.

[7] 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: 369–76.

[8] Orabona ML, Albino O. Systemic progressive sclerosis (or visceral scleroderma). Review of the literature and report of cases. Acta Med Scand 1958; 160 (Suppl): 160–70.

[9] Siegel RJ, O'Connor B, M Ena I, Criley JM. Left ventricular function at rest and during Raynaud's phenomenon in patients with scleroderma. Am Heart J 1984; 108: 1469–76.

[10] Gaffney FA, Anderson RJ, Nixon JV, Blomqvist CG, Moore Jr WE. Cardiovascular function in patients with progressive systemic sclerosis (scleroderma). Clin Cardiol 1982; 5: 569–76.

[11] Subcommittee for scleroderma criteria of American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581–90.

[12] Wikstrand J, Berglund G, Wilhelmsen L, Wallentin I. Value of systolic and diastolic time intervals. Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction. Br Heart J 1978; 40: 256–67.

[13] American Heart Association: Recommendation for human blood pressure. Determination by sphygmomanometer. Circulation 1980; 62: 1145A–55A.

[14] Caidahl K, Svärdsudd K, Eriksson H, Wilhelmsen L. Relation of dyspnea to left ventricular wall motion disturbances in a population of 67-year-old men. Am J Cardiol 1987; 59: 1277–82.

[15] Caidahl K, Eriksson H, Hartford M, Wikstrand J, Wallentin I, Svärdsudd K. Dyspnoea of cardiac origin in 67-year-old men: I. Relation to systolic left ventricular function and wall stress. The study of men born in 1913. Br Heart J 1988; 59: 319–28.

[16] Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiography determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425–31.

[17] Ihlen H, Pamile JP, Dale J *et al.* Determination of cardiac output by Doppler echocardiography. Br Heart J 1984; 51: 54–60.

[18] Sahn DJ, DeMaria A, Kisslo J, Weyman AI. The committee on M-mode standardization of the American Society of Echocardiology: Recommendation regarding quantitation in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation 1978; 58: 1072–8.

[19] Colan SD, Borow KM, Newmann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load independent index of myocardial contractility. J Am Coll Cardiol 1984; 4: 715–24.

[20] Lew W, Henning H, Schelbert H, Karliner JS. Assessment of mitral E point-septal separation as an index of left ventricular performance in patients with acute and previous myocardial infarction. Am J Cardiol 1978; 41: 836–45.

[21] Caidahl K, Svärdsudd K, Eriksson H *et al.* Dyspnea of cardiac origin in 67-year-old men: relation to clinical and non-invasive measures of cardiac function. Am J Noninv Cardiol 1988; 2: 59–68.

[22] Grossman W, Jones D, MacLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1987; 8: 384–94.

[23] Borow KM, Green LH, Grossman W, Branwald E. Left ventricular end-systolic stress shortening and stress-length relation in humans. Normal values and sensitivity inotropic state. Am J Cardiol 1982; 50: 1301–8.

[24] Hatle L, Angelsen B. Doppler ultrasound in cardiology: physical principles and clinical application. Second edition. Philadelphia: Lea & Febiger, 1986.

[25] Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. Pediatr Cardiol 1987; 8: 241–6.

[26] Leinwand I, Duryee AW, Richter MN. Scleroderma (based on a study of over 150 cases). Ann Intern Med 1954; 41: 1003–41.

[27] James TN. VIII. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974; 50: 844–56.

[28] Bulkley BH, Klacsmann PG, Hutchins GM. Angina pectoris, myocardial infarction and sudden cardiac death with normal coronary arteries: A clinicopathologic study of 9 patients with progressive systemic sclerosis. Am Heart J 1978; 95: 563–9.

[29] Follansbee WP, Curtiss EI, Medsger TA *et al.* Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N Engl J Med 1984; 310: 142–8.

[30] Kahan A, Nitenberg A, Foult JM *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985; 28: 637–45.

[31] Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. Lancet 1989; ii: 475–9.

[32] Eggebrecht RF, Kleiger RE. Echocardiographic pattern in scleroderma. Chest 1977; 71: 47–51.

[33] Child JS, Krivokapich J, Perloff JK. Effect of left ventricular size on mitral E point to ventricular septal separation in assessment of cardiac performance. Am Heart J 1981; 101: 797–804.

[34] Ahmadpour H, Shah AA, Allen JW *et al.* Mitral E point septal separation: a reliable index of left ventricular performance in coronary artery disease. Am Heart J 1983; 106: 21–8.

[35] Caidahl K, Larsson S, Südow G, Wallentin I, Angelhed J-E, Olsson SB. Conservative surgery for mitral valve prolapse with regurgitation: clinical follow-up and noninvasive assessment. Eur Heart J 1987; 8: 384–94.

[36] Kazzam E, Johansson C, Waldenström A, Hällgren R, Caidahl K. Doppler findings of mitral regurgitation and impaired left ventricular filling properties in systemic sclerosis. J Am Coll Cardiol 1990; 15 (Suppl): 273A (Abstr).

[37] Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in systemic sclerosis. J Int Med 1990; 228: 183–92.

[38] Carabello BA, Spann JF. The uses and limitations of end-systolic indexes of left ventricular function. Circulation 1984; 69: 1058–64.

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Non-invasive assessment of systolic left ventricular function in systemic sclerosis

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KEY WORDS: Doppler, echocardiography, left ventricle, systemic sclerosis, systolic function, time intervals, wall stress.

Systemic sclerosis is a multisystemic disorder, also affecting the heart. To evaluate its influence on systolic left ventricular (LV) function, we investigated 30 consecutive patients (age 54·5±2·4 years, 15 men and 15 women) and 48 controls matched for age and sex. All subjects were investigated by phonocardiography, pulse curve recordings, M-mode echocardiography, and by pulsed and continuous wave Doppler. Heart rate, blood pressure and peripheral resistance did not differ, but patients weighed less than controls (P<0·01). Systolic time intervals indicated systolic impairment, with an increased pre-ejection period to LV ejection time (LVET) ratio (0·37±0·02 vs 0·30±0·01 P<0·001), and also an increased isovolumic contraction time to LVET ratio (0·17±0·02 vs 0·12±0·01, P<0·02). The latter difference remained when LVET was adjusted for heart rate. Echocardiographic E-point to septal separation was increased in patients (8·3±1·3 vs 4·8±0·3 mm, P=0·001), also after adjustment for LV dimension (P=0·0001), while septal fractional thickening was decreased (P<0·01). End systolic wall stress (P=0·0002) and stress to volume ratio (P=0·03) were lower in systemic sclerosis. Peak LV emptying rate was also lower in the patient group when measured by echocardiography (P=0·03). There was no difference between groups regarding LV dimensions, fractional shortening or mean velocity of circumferential fibre shortening. While aortic Doppler peak emptying rate did not differ between groups, it occurred later in systole in the patient group (P<0·01) as did peak velocity (P=0·0001). Cardiac output did not differ between the groups. In all, 18 of 30 patients (60%) had a systolic abnormality. However, only one patient had dilated cardiomyopathy, and two other patients had poor systolic function without LV dilatation. There was no relation between disease duration and systolic LV function.

We conclude that, in a consecutive series of patients with systemic sclerosis, systolic LV function is frequently impaired. While time intervals, emptying rate, and wall fractional thickening are affected, cardiac output and LV cavity dimensions are usually not.

Introduction

Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin. Visceral involvement is also well recognized, particularly the lungs, heart, kidneys and the gastrointestinal tract[1]. Cardiac involvement has, since it was reported by Weiss *et al.* in 1943[2], been a subject of wide interest[3–6]. Involvement of the heart in systemic sclerosis is associated with poor prognosis[7–8]. Since myocardial impairment may escape clinical detection, it seems important to apply methods with the potential to reveal cardiac dysfunction. However, results from non-invasive studies of systolic function in systemic sclerosis are somewhat contradictory[9,10].

We therefore studied a series of 30 consecutive patients to evaluate the presence and extent of left ventricular (LV) systolic dysfunction in systemic sclerosis and related the results to those of matched controls.

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Subjects and methods

SUBJECTS

We studied 30 consecutive patients (15 men and 15 women) with systemic sclerosis according to the American Rheumatology Association (ARA) criteria[11]. The patients were referred from The Uppsala region to Uppsala University Hospital between December 1986 and March 1988. Their mean age was 54·5 (range 25–77) years, and their disease had been recognized for 5·6 (range 0·5–23) years. General characteristics are shown in Table 1. Three randomly selected patients, and the patient with the largest reversible perfusion defect shown by myocardial scintigraphy after cold provocation, were subjected to coronary arteriography, but none of the four patients demonstrated abnormal angiograms. One patient had right bundle branch block, while none was found to have left bundle branch block.

For comparative purposes, age- and sex-matched control subjects were selected from the general population of Uppsala. Every resident in Sweden has a national registration number that includes date of birth. The numbers are registered by the County Census Bureau in a population register, which includes vital statistics, and which by law must be kept up to date. A sample of 90 age- and

Table 1 Characteristics of controls and patients

	Controls ($N=48$)	Patients ($N=30$)	P
Age (years)	54·6±2·1	54·5±2·4	N.S.
Sex (female/male)	22/26	15/15	N.S.
Height (cm)	172·7±1·11	170·9±1·9	N.S.
Weight (kg)	72·6±1·7	65·1±2·0	0·01
Body surface area (m^2)	1·9±0·03	1·7±0·04	0·02
Body mass index ($kg\ m^{-2}$)	24·3±0·5	22·3±0·9	0·008
Systolic blood pressure (mmHg)	134·9±2·6	132·9±3·5	N.S.
Diastolic blood pressure (mmHg)	81·4±1·4	78·7±2·1	N.S.
Mean arterial blood pressure (mmHg)	99·3±1·5	96·8±2·1	N.S.
Total peripheral resistance ($dyn.s.cm^{-5}$)	1604±59	1723±132	N.S.

Values are mean ±S.E. N.S. = not significant.

sex-matched subjects (three for each patient) was drawn from the register. All 90 controls were informed about the investigation protocol, and 55 of them gave their consent to participate in the study. Controls were excluded if treated for hypertension, and if clinical history or electrocardiography revealed coronary or rheumatic heart disease. Controls were not excluded on the basis of blood pressure level. No control had bundle branch block. None had known renal or pulmonary disease. Of the 55 subjects willing to participate, two were excluded due to previous antihypertensive treatment, one due to an electrocardiogram (ECG) indicating coronary heart disease, one due to a clinical history suggestive of ischaemic heart disease, two subjects because of a history of rheumatic heart disease, and one subject because of inadequate recordings. The remaining 48 subjects (26 men and 22 females) had a mean age of 54·6 (range 25–77) years and were included as a healthy control group.

METHODS

A standard 12-lead resting ECG, pulse curves and phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as previously described[12]. In brief, simultaneous carotid pulse tracing, ECG (standard lead II) and a phonocardiogram from the third left parasternal intercostal space, were recorded at 100 mm s^{-1} at the end of normal relaxed expiration with the subject in the supine position. Apex-cardiographic registrations were obtained similarly, but with the patient lying in the left lateral position.

Blood pressure was recorded in the supine position after 30 min of rest, after pulse recordings and immediately before M-mode recordings. Standard sphygmomanometer technique was applied, and the mean of three readings was used. Systolic blood pressure was measured at phase one and diastolic blood pressure at the disappearance of Korotkoff sound-phase five[13].

Echocardiography was performed by means of a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2·5 or 3·5 MHz phased array transducer. Parasternal two-dimensional (2-D) echocardiographic views[14] were stored on VHS 0·5 inch video tapes by means of a Panasonic video recorder NV 8100. Two-D guided M-mode echocardiograms[15] were recorded on strip charts (Honeywell, 8100, dry Silver paper) at a speed of 50 $mm.s^{-1}$. These investigations were performed with the subject lying in the left lateral position.

To measure cardiac output[16,17], a Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record the aortic flow spectrum. A 2 MHz single crystal pulsed and continuous wave Doppler probe with a diameter of 13·7 mm was used. The examination was carried out with patients lying in the left lateral position using an apical approach. The area of the maximum LV apex pulsation was defined, and the transducer was placed slightly above, slightly below or directly over it. Both continous and pulsed wave Doppler spectrum were recorded, guided by the Doppler signal of valve closure and opening. The audible Doppler sound pattern from the blood flow was also used, and the transducer was manipulated until the best spectral display was obtained from the aortic flow. Strip chart recordings were obtained at a speed of 50 $mm.s^{-1}$.

MEASUREMENTS

All measuring points were agreed upon by two observers (E.K. and K.C.). One investigator (E.K.) carried out all interpretations after the recordings had been coded and mixed (by K.C.). Only beats with acceptable or good quality were used for measurements.

From M-mode echocardiographic recordings the measurements listed below were made on three beats (leading edge to leading edge method) according to the recommendations made by the American Society of Echocardiography[18], and the mean was used for further calculations. LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-diastole (the electrocardiographic Q wave), and at end-systole (the shortest distance between the septum and the posterior wall). M-mode echocardiographic dimensions and time intervals as well as amplitudes from pulse tracings were measured by means of a digitizing table-minicomputer system.

LV wall fractional thickening was calculated as septal and posterior wall systolic increase of thickness, respectively, divided by the corresponding diastolic thickness. Fractional shortening was defined as the difference between LV diastolic and systolic dimensions divided by the diastolic dimension. Ejection fraction was calculated according to the cube formula, for reasons discussed elsewhere[15]. Mean velocity of circumferential fibre shortening (mean Vcf) was calculated as fractional shortening divided by LV ejection time (LVET). Mean Vcf adjusted for heart rate (mean Vcf_c) was calculated as fractional shortening divided by LVET normalized by the square root of the cardiac cycle length in seconds[19]. Mitral E-point to septal separation (EPSS) was defined as the vertical distance (mean of five beats) between the E point of the anterior mitral leaflet and the ventricular septum[20,21]. EPSS was adjusted for end-diastolic LV dimension.

LV meridional end-systolic wall stress (ESWS) (10^3.dyn.cm^{-2}) was estimated as ESWS = (1·332 × pressure × D)/[4h × (1 + h/D)], where D represents LV end-systolic dimension and h stands for the mean of the septal and posterior wall end-systolic thickness[15,22]. Pressure was obtained by estimating end-systolic blood pressure from the carotid pulse tracing, where systolic and diastolic blood pressures were assigned to the peak and nadir of the carotid curve, respectively, and end-systolic blood pressure was estimated by linear interpolation to the height of the dicrotic notch[23]. End-systolic volume index (ESVI) was calculated as end-systolic volume/body surface area. As a measure of contractility, we also calculated the ratio ESWS/ESVI. The mean Vcf_c to be expected from the level of ESWS was calculated by means of the regression formula obtained from the relation between these two variables in the control group. The ratio between measured and expected mean Vcf_c was calculated as percentage (mean Vcf_c%).

From M-mode recordings, LV peak emptying rate as well as time from the electrocardiographic R-wave to peak emptying rate were measured by means of a digitizing table (Summagraphics ID-2CTR-TAB 17, Connecticut, U.S.A.) and a microcomputer (Professional-380, Digital Equipment Corp., U.S.A.), using an especially designed computer programme[15]. The same equipment was used for the evaluation of Doppler recordings. Measurements of aortic Doppler (pulsed and continuous) registrations were performed on five beats, and the mean value was used. Maximum LV emptying velocity was measured. Stroke volume was calculated as the velocity integral of pulsed Doppler systolic aortic flow, multiplied by the aortic area[24,25], where the latter was calculated at π(dimension/2)^2 from the aortic diameter (leading edge) just below the insertion of the aortic leaflets in parasternal 2-D echocardiographic projection.

Mean arterial pressure (MAP) was calculated according to the formula (systolic − diastolic blood pressure)/3 + diastolic blood pressure. Total peripheral resistance (TPR) was calculated according to the formula TPR = MAP × 1·33[60/Doppler cardiac output].

Measurements of pulse curve tracings were performed on five beats, and the mean values were used. The LVET, the electromechanical interval, the pre-ejection period (PEP) and the isovolumic contraction time (ICT), were measured as previously described, from the simultaneous recordings of the electrocardiographic lead II, the phonocardiogram and the carotid pulse tracing or apex-cardiogram[12]. Electromechanical interval and LVET were related to heart rate. LVET was therefore adjusted for heart according to the regression equation of the control group. The relative LVET was calculated as percentage of the expected normal LVET. PEP/LVET and ICT/LVET were calculated. Ratios in which LVET had been adjusted to heart rate 60 (LVET divided by square root of the cycle length in seconds) were also computed.

STATISTICAL ANALYSIS

Data are presented as mean ± standard error of the mean (SE). Unpaired two-sided t-test was used to compare differences between patients and controls. P values $< 0{\cdot}05$ were considered significant. For selected variables, abnormal values were defined by two standard deviations (SDs) of the control group.

Results

GENERAL CHARACTERISTICS

Clinical characteristics of the controls and the patients are shown in Table 1. In spite of similar heights, patients weighed less than controls as a group, and five patients had a low calculated body surface area. Blood pressure and TPR were similar in the two groups.

SYSTOLIC TIME INTERVALS

In the patient group, LVET was significantly shorter, and ICT as well as PEP were longer (Table 2). Also in the patient group, the ratios PEP/LVET and ICT/LVET were significantly higher, and differences remained when the LVET was adjusted for heart rate. Five patients had an increased PEP/LVET ratio.

ECHOCARDIOGRAPHY AND DOPPLER

When heart rate was measured during the echocardiographic investigation, patients had higher heart rates than controls (Table 3), but only one patient had a heart rate above the reference limit. Two patients had LV dilatation, but the mean values of end-diastolic and end-systolic LV internal dimensions did not differ between groups, nor did fractional shortening, mean Vcf or mean Vcf_c (Table 3). In spite of this, EPSS was larger in patients (increased in 26%). The difference regarding EPSS remained after adjustment for LV dimension. Septal fractioning thickening was reduced in systemic sclerosis, and stroke volume tended to be lower ($P = 0{\cdot}06$), as did stroke volume calculated from Doppler recordings (Table 4). ESWS was lower in the patient group (Table 3), and a difference remained when ESWS was adjusted for ESVI. Mean Vcf_c% tended to be lower in the patient group, and three patients had a reduced value. The peak rate of LV emptying, measured from M-mode echocardiography, was lower among patients (Table 3). The time from the

Table 2 Systolic time intervals

	Controls ($N=48$)	Patients ($N=30$)	P
LVET (ms)	323±4	303±6	0·007
PEP (ms)	96±3	110±5	0·01
ICT (ms)	40±3·2	51±4·2	0·04
PEP/LVET	0·30±0·01	0·37±0·02	0·0006
ICT/LVET	0·12±0·01	0·17±0·02	0·01
$PEP/LVET_c$	0·30±0·01	0·37±0·02	0·0006
$ICT/LVET_c$	0·12±0·01	0.17±0·02	0·01

Values are mean ±S.E. LVET = left ventricular ejection time; PEP = pre-ejection period; ICT = isovolumic contraction time; $LVET_c$ = left ventricular time normalized for the square root of the cardiac cycle length.

Table 3 M-mode echocardiographic measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·6±1·4	67·5±1·7	0·01
LV dimension (Q) (mm)	49·9±0·8	48·5±1·4	N.S.
LV dimension (end-systole) (mm)	32·8±0·7	32·5±1·7	N.S.
Fractional thickening			
Septum (%)	43±3	30±4	0·007
Posterior wall (%)	61±4	53±5	N.S.
Stroke volume (ml)	94·5±4·9	80·4±5·0	N.S.
Ejection fraction	0·72±0·01	0·69±0·03	N.S.
Fractional shortening (%)	34·6±0·9	33·5±1·6	N.S.
Mean Vcf (circ s^{-1})	1·07±0·03	1·11±0·05	N.S.
Mean Vcf_c (circ s^{-1} $s^{0·5}$)	1·07±0·03	1·05±0·05	N.S.
Mean Vcf_c%	98·5±1·9	92·7±2·6	N.S.
ESWS (10^3.dyn.cm^{-2})	62·9±2·2	51·3±2·8	0·002
ESVI (ml m^{-2})	20·1±1·1	19·5±1·8	N.S.
ESWS/ESVI (10^3.dyn.cm^{-1}.ml^{-1}.cm^2)	3·34±0·13	2·9±0·16	0·03
EPSS (mm)	4·8±0·3	8·3±1·3	0·001
EPSS/LV dimension (Q)	0·098±0·01	0·162±0·02	0·0001
Peak emptying rate (mm s^{-2})	−105·5±4·2	−92·0±3·4	0·03
Time R wave to peak emptying rate (ms)	201·9±9·3	188·6±11·8	N.S.
Time to peak emptying (% of systole)	68·2±3·3	67·1±4·8	N.S.

Values are mean ±S.E. N.S. = not significant. LV = left ventricular; Vcf = velocity of circumferential fibre shortening; Vcf_c = Vcf adjusted for heart rate; Vcf_c% = measured/expected (from ESWS) Vcf_c; ESWS = end-systolic wall stress; ESVI = end-systolic volume index; EPSS = E-point septal separation.

R-wave to peak emptying did not differ, but, when calculated in relation to duration of systole, peak emptying occurred later in the patient group. When calculated from continuous wave Doppler (Table 4), the time to peak aortic flow acceleration, and also the time to peak aortic flow velocity, was longer in the patient group in spite of no significant difference regarding peak velocity of LV emptying (aortic flow acceleration) as calculated from Doppler.

INDIVIDUAL ABNORMALITIES

We evaluated the number of patients with abnormal values regarding the following variables: LV end-diastole dimension, ejection fraction, Vcf_c%, PEP/LVET, ICT/LVET, ESWS/ESVI, EPSS, time to peak aortic flow velocity and acceleration. Altogether, 18 patients (60%) had one or more abnormal findings regarding these variables. The variables displaying the highest prevalence of abnormal values were EPSS, time to peak flow velocity, PEP/LVET, and time to aortic peak flow acceleration. There was no significant relation between these variables and disease duration.

One patient had findings of dilated cardiomyopathy with a dilated left ventricle (77 mm) and a low ejection fraction (22%). Two other patients had low ejection fraction and low Vcf_c% in spite of LV dimension within the reference limits. Two patients had isolated abnormality of systolic time intervals and two patients isolated increase of EPSS.

Discussion

The present study is the first to compare LV function, in a consecutive series of patients with systemic sclerosis,

Table 4 Doppler measurements

	Controls ($N=48$)	Patients ($N=30$)	P
Heart rate (beats min^{-1})	61·4±1·1	69·0±2·1	0·0008
Stroke volume (ml)	74·4±2·8	67·5±5·0	N.S.
Cardiac output (l min^{-1})	4·6±0·2	4·5±0·3	N.S.
Peak aortic gradient (mmHg)	5·3±0·4	5·0±0·5	N.S.
Time to peak velocity (% of systole)	25·0±0·8	31·7±1·6	0·0001
Peak acceleration (mmHg s^{-1})	111±6	104±11	N.S.
Time to peak acceleration (% of systole)	9·1±0·3	10·6±0·6	0·01

Values are mean ±S.E. N.S. = not significant.

with that of a random sample of matched control subjects from the general population. Great care was taken to ensure objective evaluation of data. Thus, the investigations were all carried out by the same investigator, who was unaware of the clinical findings. Interpretations were likewise performed by a single investigator, after blind-coding and mixing of the recordings from patients and controls.

Focal myocardial fibrosis reported by several authors[3,5,26], may be the reason for the development of myocardial dysfunction in systemic sclerosis. However, even patients with systemic sclerosis who died suddenly seem to display conspicuously normal extramural coronary arteries at autopsy[27,28]. Focal myocardial lesions have no relation to specific extramural vasculature[3], and myocardial necrosis occurs with widely patent intramural and extramural coronary arteries, suggesting the microcirculation is abnormal[28–30]. Although patients with arrhythmias and conduction disturbances who die suddenly have abnormalities of their sinus node artery and AV-node artery[27], an autopsy study of 52 patients have shown intramural coronary arteries to be generally normal histologically and microangiograms in 12 patients to be free from abnormalities[3]. Vasospasm or myocardial Raynaud's phenomenon have been suggested to be responsible for the myocardial necrosis seen in systemic sclerosis[28,29], and we were recently able to substantiate this hypothesis by showing in the present study group reversible myocardial perfusion defects induced by cold provocation[31]. Since in the patient with the largest myocardial perfusion defects arteriography showed normal coronary arteries, as did the angiograms from three randomly selected patients, we considered coronary arteriography to be neither necessary nor ethical in the remainder of the present study population. Moreover, we could not, for ethical reasons, have made comparative studies in the control group.

Some patients with systemic sclerosis develop severe cardiac involvement with a picture of dilated cardiomyopathy[32]. Such findings are, however, rare and were only seen in one patient in the present study, while two other patients had low ejection fraction without dilatation. Most patients had only a mild or moderate impairment of systolic function. Thus, the mean values of ejection fraction did not differ between the groups.

The systolic time intervals of the patients were clearly abnormal. One possible explanation for this is inclusion of patients with bundle branch block, while controls had normal transmission of depolarization potentials. Such an explanation was, however, not valid, since only one patient had right bundle branch block, and none had left bundle branch block. A more plausible explanation of abnormal systolic time intervals is obviously a true myocardial impairment.

The existence of myocardial dysfunction was substantiated by the findings of increased EPSS (with and without adjustment for LV dimension), reduced septal fractional thickening, reduced LV emptying by M-mode digitization, and delayed times to peak aortic flow acceleration and velocity by Doppler. The time for aortic flow to peak acceleration and velocity may be more sensitive indicators of contractility than peak acceleration, although also the latter tended to be abnormal.

We used EPSS in the present study since this measure has been shown to be a valid predictor of depressed systolic function independent of LV size and wall motion abnormalities, and better than other echocardiographic indices correlated to angiographic ejection fraction[20,33,34]. Mitral regurgitation causing a low afterload in the patient group is one possible explanation for the lack of difference between groups regarding fractional shortening and similar indices[35]. Although, Doppler evidence of mild mitral insufficiency was prevalent, moderate or severe regurgitation was rare (two patients) in systemic sclerosis (any degree of regurgitation found in 40% of patients vs 4% in the control group, $P<0·001$)[36], a low afterload being more probably explained by systolic impairment together with an increased relative wall thickness among patients[37]. The ratio ESWS/ESVI takes load into account, and a low value of this ratio indicates systolic impairment irrespective of mitral regurgitation[38]. Thus, the difference between groups regarding ESWS/ESVI means systolic impairment in the patient group.

We conclude that the systolic LV function in many patients with systemic sclerosis is impaired to a mild or moderate degree. The prevalence of more advanced involvement is low, possibly because of rapid deterioration in such cases. However, myocardial dysfunction seems to be detectable at an early stage when it could still be influenced by medical therapy. The cardiac effects of

treatment with angiotensin-converting-enzyme inhibitors is currently being evaluated in the present study population.

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References

[1] Medsger TA Jr. Systemic sclerosis (Scleroderma), eosinophilic fasciitis, and calcinosis. In: McCarthy DJ, Ed. Arthritis and allied conditions. A textbook of rheumatology. Philadelphia: Lea & Febiger, 1985, 994–1036.

[2] Weiss S, Stead EA, Warren JV, Bailey OT. Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma. Arch Intern Med 1943; 71: 749–76.

[3] Bulkley BH, Ridolfi RL, Slayer ER, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976; 53: 483–90.

[4] Mac Whorter JE, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). Am J Med 1974; 57: 566–75.

[5] Sackner MA, Heinz ER, Steinberg AJ. The heart in scleroderma. Am J Cardiol 1966; 17: 542–75.

[6] Gottdiener Moutsopoulos HM, Decker JL. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979; 66: 391–8.

[7] 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: 369–76.

[8] Orabona ML, Albino O. Systemic progressive sclerosis (or visceral scleroderma). Review of the literature and report of cases. Acta Med Scand 1958; 160 (Suppl): 160–70.

[9] Siegel RJ, O'Connor B, M Ena I, Criley JM. Left ventricular function at rest and during Raynaud's phenomenon in patients with scleroderma. Am Heart J 1984; 108: 1469–76.

[10] Gaffney FA, Anderson RJ, Nixon JV, Blomqvist CG, Moore Jr WE. Cardiovascular function in patients with progressive systemic sclerosis (scleroderma). Clin Cardiol 1982; 5: 569–76.

[11] Subcommittee for scleroderma criteria of American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581–90.

[12] Wikstrand J, Berglund G, Wilhelmsen L, Wallentin I. Value of systolic and diastolic time intervals. Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction. Br Heart J 1978; 40: 256–67.

[13] American Heart Association: Recommendation for human blood pressure. Determination by sphygmomanometer. Circulation 1980; 62: 1145A–55A.

[14] Caidahl K, Svärdsudd K, Eriksson H, Wilhelmsen L. Relation of dyspnea to left ventricular wall motion disturbances in a population of 67-year-old men. Am J Cardiol 1987; 59: 1277–82.

[15] Caidahl K, Eriksson H, Hartford M, Wikstrand J, Wallentin I, Svärdsudd K. Dyspnoea of cardiac origin in 67-year-old men: I. Relation to systolic left ventricular function and wall stress. The study of men born in 1913. Br Heart J 1988; 59: 319–28.

[16] Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiography determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425–31.

[17] Ihlen H, Pamile JP, Dale J *et al.* Determination of cardiac output by Doppler echocardiography. Br Heart J 1984; 51: 54–60.

[18] Sahn DJ, DeMaria A, Kisslo J, Weyman AI. The committee on M-mode standardization of the American Society of Echocardiology: Recommendation regarding quantitation in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation 1978; 58: 1072–8.

[19] Colan SD, Borow KM, Newmann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load independent index of myocardial contractility. J Am Coll Cardiol 1984; 4: 715–24.

[20] Lew W, Henning H, Schelbert H, Karliner JS. Assessment of mitral E point-septal separation as an index of left ventricular performance in patients with acute and previous myocardial infarction. Am J Cardiol 1978; 41: 836–45.

[21] Caidahl K, Svärdsudd K, Eriksson H *et al.* Dyspnea of cardiac origin in 67-year-old men: relation to clinical and non-invasive measures of cardiac function. Am J Noninv Cardiol 1988; 2: 59–68.

[22] Grossman W, Jones D, MacLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1987; 8: 384–94.

[23] Borow KM, Green LH, Grossman W, Branwald E. Left ventricular end-systolic stress shortening and stress-length relation in humans. Normal values and sensitivity inotropic state. Am J Cardiol 1982; 50: 1301–8.

[24] Hatle L, Angelsen B. Doppler ultrasound in cardiology: physical principles and clinical application. Second edition. Philadelphia: Lea & Febiger, 1986.

[25] Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. Pediatr Cardiol 1987; 8: 241–6.

[26] Leinwand I, Duryee AW, Richter MN. Scleroderma (based on a study of over 150 cases). Ann Intern Med 1954; 41: 1003–41.

[27] James TN. VIII. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974; 50: 844–56.

[28] Bulkley BH, Klacsmann PG, Hutchins GM. Angina pectoris, myocardial infarction and sudden cardiac death with normal coronary arteries: A clinicopathologic study of 9 patients with progressive systemic sclerosis. Am Heart J 1978; 95: 563–9.

[29] Follansbee WP, Curtiss EI, Medsger TA *et al.* Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N Engl J Med 1984; 310: 142–8.

[30] Kahan A, Nitenberg A, Foult JM *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985; 28: 637–45.

[31] Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. Lancet 1989; ii: 475–9.

[32] Eggebrecht RF, Kleiger RE. Echocardiographic pattern in scleroderma. Chest 1977; 71: 47–51.

[33] Child JS, Krivokapich J, Perloff JK. Effect of left ventricular size on mitral E point to ventricular septal separation in assessment of cardiac performance. Am Heart J 1981; 101: 797–804.

[34] Ahmadpour H, Shah AA, Allen JW *et al.* Mitral E point septal separation: a reliable index of left ventricular performance in coronary artery disease. Am Heart J 1983; 106: 21–8.

[35] Caidahl K, Larsson S, Südow G, Wallentin I, Angelhed J-E, Olsson SB. Conservative surgery for mitral valve prolapse with regurgitation: clinical follow-up and noninvasive assessment. Eur Heart J 1987; 8: 384–94.

[36] Kazzam E, Johansson C, Waldenström A, Hällgren R, Caidahl K. Doppler findings of mitral regurgitation and impaired left ventricular filling properties in systemic sclerosis. J Am Coll Cardiol 1990; 15 (Suppl): 273A (Abstr).

[37] Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in systemic sclerosis. J Int Med 1990; 228: 183–92.

[38] Carabello BA, Spann JF. The uses and limitations of end-systolic indexes of left ventricular function. Circulation 1984; 69: 1058–64.