Non-invasive assessment of early cardiac involvement in systemic sclerosis

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Summary: Twenty-eight patients with wide spectrum organ involvement of progressive systemic sclerosis but without signs or symptoms suggestive of cardiac involvement were studied by non-invasive cardiac techniques. The 12-lead electrocardiogram showed abnormalities in 6 patients: one had abnormal T waves and 5 had complete or incomplete right bundle branch block. Twenty four hour ambulatory electrocardiography demonstrated higher average heart rates than in similar aged controls (82 ± 9 vs 74 ± 9 beats/min, $P < 0.05$). In one patient a short run of ventricular tachycardia was recorded. No other significant arrhythmia was documented. Echocardiographic measurements were within normal ranges but small pericardial effusions were observed in two patients (7%). Resting first pass radionuclide angiography, utilizing 12 mCi of technetium 99m were performed in 23 patients. Seven patients (30%) had abnormal wall motion (diffuse hypokinesia), with a significant decrease in ejection fraction in comparison to those with normal wall motion ($44 \pm 6\%$ vs $60 \pm 6\%$ $P < 0.01$). Those with abnormal wall motion had suffered the disease longer than those with normal wall motion (13 ± 4 vs 9.5 ± 7 y). In conclusion, the heart is involved in half of the patients in this series; non-invasive cardiac assessment is useful in disclosing the early cardiac involvement and may influence long-term management.

Introduction

Systemic sclerosis is a disease of unknown aetiology characterized by excessive fibroblastic activity and collagen deposition which can involve several organs of the body, including the heart. Pathological studies have revealed in 12–80% of cases that fibrosis can occur in any part of the heart (D'Angelo *et al.*, 1969; Bulkley *et al.*, 1976), but it is often clinically unrecognized (Botstein & Le Roy, 1981). The early detection of cardiac involvement may have important prognostic implications as sudden cardiac death has been associated with this disease (Marinato *et al.*, 1981; Oram & Stokes, 1961; Bulkley *et al.*, 1978; James, 1974; Roberts & Cabeen, 1980). In this study 28 patients with a wide spectrum of organ involvement by systemic sclerosis but with no cardiac symptoms were studied by electrocardiography, echocardiography and nuclear scintigraphy in order to discover early cardiac involvement.

Methods

Patients

Twenty eight patients, 21 women and 7 men, with systemic sclerosis were studied. The mean age was 48 ± 13 y (mean $\pm$ s.d.) and the patients had suffered from systemic sclerosis for a mean of 11 ± 6 y. Table I shows the clinical details of the patients and the spectrum of organ involvement which was discovered either clinically or during investigation. Skin involvement was subdivided into calcification, sclerosis and telangiectasia. Raynaud's phenomenon was investigated by thermography including a cold stress test. Gastrointestinal and pulmonary involvement were diagnosed clinically, radiologically and by pulmonary function tests. Renal function was assessed by estimation of blood urea, serum electrolytes, serum creatinine and a creatinine clearance test. Metabolic studies included liver function tests, blood glucose, serum calcium and phosphate levels. Musculoskeletal involvement was detected by examination of stiffness, fixity and range of joint movement. Non-specific

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Table I The clinical data of patients involved in this study

No.	Age	Sex	Duration	Skin			Ren	GIT	Pul	Renal	Muscular Skeletal	Metab	Non sp
				C	S	T							
1	46	F	2	-	+	+	+	+	+	-	+	-	+
2	54	F	20	-	+	+	+	+	-	-	+	-	-
3	52	F	20	-	+	+	+	-	-	-	-	-	-
4	70	F	20	-	+	+	+	+	-	-	+	-	+
5	54	F	3	+	+	+	+	+	+	+	+	+	+
6	31	F	10	-	+	+	+	+	-	-	-	-	-
7	45	M	2	-	+	+	+	-	-	-	+	-	-
8	20	M	10	-	+	-	+	-	+	-	+	-	-
9	42	F	15	+	+	-	+	-	-	+	+	-	-
10	37	F	10	-	+	-	+	-	+	-	-	-	-
11	36	F	10	-	+	+	+	+	-	-	-	-	-
12	32	M	1	+	+	+	+	+	+	-	-	-	-
13	54	F	15	-	+	+	+	+	-	-	-	-	+
14	50	F	6	+	+	+	+	+	+	-	+	-	+
15	53	M	2	-	+	-	+	-	-	-	-	-	-
16	63	F	7	-	+	+	+	+	-	-	-	-	-
17	38	F	9	-	-	+	+	-	-	-	-	-	-
18	41	F	22	-	+	-	-	-	+	-	-	+	-
19	30	F	9	+	+	+	+	+	+	-	+	-	+
20	50	F	14	-	+	+	+	+	+	-	+	-	+
21	70	F	16	-	+	+	+	-	-	-	+	-	+
22	54	F	9	+	+	+	+	+	+	-	+	-	+
23	65	F	20	-	+	+	+	+	+	-	-	-	-
24	43	F	5	-	+	+	-	+	-	-	-	-	-
25	59	M	6	-	+	+	+	+	-	-	-	-	-
26	51	F	5	+	-	-	+	+	-	-	-	+	+
27	66	M	12	+	+	+	+	+	+	-	-	-	-
28	45	M	15	+	+	+	+	+	-	-	-	-	+

C = calcification; S = sclerosis; T = telangiectasia; Ren = Raynaud's phenomenon; GIT = gastrointestinal tract; Pul = pulmonary; Metab = metabolic abnormalities; Non-sp = non specific (see text).

symptoms included malaise, weakness, lassitude and anorexia.

Protocol of the study

The study was performed on an outpatient basis. Informed consent was obtained in all cases.

Electrocardiographic study

A 12-lead electrocardiogram was obtained from each patient. Twenty four hour ambulatory electrocardiograms were recorded using a 'Tracker' 24 h tape recorder. The tapes were then analysed by a Pathfinder analyser (Reynolds Medical, UK). The hourly minimum, maximum and average heart rates and 24 h trends were obtained. The electrocardiographic criteria used in this study were defined according to the Minnesota code (Prineas *et al.*, 1982) and the rhythm disturbances were defined as follows: Sinus tachycardia: sinus rate of 120 beats/min or more. Sinus bradycardia: sinus rate of 50 beats/min or less. Sinus

arrhythmia: > 20% variation of RR interval from the preceding cycle. Sinus pause: PP interval more than 1.7 s. Ventricular ectopics were classified according to Lown's classification (Lown & Wolf, 1971). Ventricular tachycardia: more than 5 successive ventricular beats at a rate more than 120 beats/min.

Echocardiographic study

On the day of the electrocardiographic study an M mode echocardiogram was performed in both the supine and the semi left lateral position. Recording of all cardiac chambers and valves was attempted. The echocardiographic measurements were according to the recommendation of the American Society of Echocardiography (Sahn *et al.*, 1978).

Nuclear angiogram

Resting first pass radionuclide angiography was performed on the same or the following day as the above studies. A bolus of 12 mCi of technetium-99m as

perchnetate was injected through an ante-cubital vein followed by a rapid 20 ml saline flush. The dynamic data were collected at 30 ms framing intervals and the counts continued for 1000 frames (for 30 s), using a computerized multicrystal gamma camera (Baird Corporation, System 77). All studies were performed in the anteroposterior projection and data were corrected for flood field non-uniformity and instrument dead-time (Dymond *et al.*, 1979). Total left ventricular ejection fraction (LVEF) was calculated from the background corrected activity curve generated from the LV region of interest. Regional wall motion was estimated visually by superimposing end systolic and end diastolic perimeters and from regional ejection fraction images (Dymond *et al.*, 1980).

Results

Electrocardiography

Surface 12-lead electrocardiogram Six patients had abnormalities in their 12-lead electrocardiogram. In one patient there were Q waves and flat T waves in V4–V6, in 2 patients there was right bundle branch block (RBBB) and in 3 patients there was incomplete RBBB.

Heart rate changes during 24-hour monitoring The average heart rate during the 24 hour recording in all patients was 82 ± 9 beats/min with a range of 59 ± 9 to 122 ± 17 beats/min. The mean heart rate was significantly higher ($P < 0.05$) than that of a standard middle-aged population of normal males and females (74 ± 9 , range 53–95 beats/min; Bjerregaard, 1983). This observation held true for both waking and sleeping periods (awake: 83 ± 13 compared with asleep: 71 ± 10 beats/min).

Cardiac arrhythmias Sinus rhythm was predominant in all patients in this study. In 14% of the patients isolated atrial premature complexes were seen. Two patients had an occasional bout of atrial fibrillation for 2–4 s. One had sporadic 5:4 atrioventricular Wenckebach block during sleep only and one other had occasional Mobitz II AV block. One patient had one short run (3 s) of ventricular tachycardia (Table II).

Echocardiography

The echocardiographic measurements in these patients were within normal limits (Table III). No abnormalities were seen in wall or valve motion. Fourteen patients (50%) showed some evidence suggestive of a thickened pericardium according to the criteria of Schnittger *et al.* (1978) but there was no evidence of constrictive pericarditis. The mean mitral

Table II The spectrum of cardiac arrhythmia in patients involved in this study

Rhythm	No. of patients	Percentage
Sinus tachycardia	18	64
Sinus bradycardia	3	11
Sinus pauses (> 1.7 s)	0	0
Sino-atrial block	1	4
Sinus arrhythmia	7	25
<i>Supraventricular arrhythmia</i>		
Atrial premature beats	4	14
Atrial fibrillation	2	7
Mobitz II AV block	1	4
Wenckebach AV block	1	4
<i>Ventricular arrhythmia</i>		
VPC < 30 /h	8	29
VPC > 30 /h	2	7
Multimorphological VPC	1	4
Couplets	1	4
R on T	0	0
Ventricular tachycardia	1	4

VPC = ventricular premature complexes; AV = atrioventricular.

EF slope in these patients was 8.1–16.5 cm/s. A small pericardial effusion was demonstrated in 2 patients (7%) associated in both cases with echocardiographic evidence of pericardial thickening.

Left ventricular nuclear angiography

Twenty three patients had nuclear angiographic studies (5 declined this part of the study). The mean ejection fraction was $56 \pm 9\%$ (range 39–65%). Seven patients (30%; Table IV) showed wall motion abnormalities. The duration of illness for patients having

Table III Echocardiographic measurements in asymptomatic patients with systemic sclerosis

LVIDd	4.27 ± 0.61 cm
LVIDs	2.76 ± 0.46 cm
IVS	0.93 ± 0.02 cm
LVPW	0.89 ± 0.02 cm
Aorta	2.79 ± 0.46 cm
LA	2.65 ± 0.46 cm
Mitral EF slope	9.08 ± 2.60 cm
RV	1.88 ± 0.57 cm
Ejection time	0.30 ± 0.03 s

LVIDd = left ventricular internal dimension during diastole; LVIDs = left ventricular internal dimension during systole; IVS = interventricular septum; LVPW = left ventricular posterior wall motion; LA = left atrial dimension; RV = right ventricular dimension; EF = ejection fraction.

Table IV Clinical and nuclear angiographic data of 7 patients having abnormal nuclear angiographic findings

Patient no.	Age	Duration of illness	Wall motion	Ejection fraction (%)	ECG
9	42	15	diffuse hypokinesia	42	Normal
10	37	10	diffuse hypokinesia	55	flat Tv4, V6 & Q wave
20	50	14	diffuse hypokinesia	49	Normal
21	70	16	diffuse hypokinesia (mainly antero apical)	48	Normal
24	43	5	diffuse hypokinesia	39	Normal
27	66	12	diffuse hypokinesia	39	Normal
28	42	15	diffuse hypokinesia	39	Normal

normal wall motion was 9.5 ± 7 y while for those having abnormal wall motion it was 13 ± 4 y. In the abnormal wall motion group ejection fraction was reduced to $44 \pm 6\%$ compared to $60 \pm 6\%$ of the group with normal wall motion ($P < 0.01$). Only 2 patients with normal wall motion had an ejection fraction of less than 55% (49% and 51%) which is the lower limit of normal in our laboratory. There was no significant difference in the mean age of the two groups (50 ± 13 y for those having normal wall motion and 44 ± 9.5 y for those with abnormal wall motion).

All but one of the patients with wall motion abnormalities had a normal 12-lead electrocardiogram. In one case there were Q waves and inverted or flat T waves in V4–V6. The 24 hour electrocardiogram revealed no difference in heart rate between the two groups. Diffuse wall motion abnormalities were observed in the patient who had ventricular tachycardia on the 24 hour electrocardiogram.

Discussion

In this non-invasive assessment of cardiac structure and function 15 of 28 (54%) asymptomatic cardiac patients with progressive systemic sclerosis had some kind of otherwise occult cardiac involvement.

Fibrotic lesions of the myocardium suggestive of systemic sclerosis had been observed in 12–80% of patients from different series (D'Angelo *et al.*, 1969; Bulkley *et al.*, 1976; Botstein & LeRoy, 1981; Sackner, 1966). Fibrosis may result in different clinical presentations including angina, myocardial infarction and arrhythmias even in the presence of normal coronary arteries (Bulkley *et al.*, 1976; Oram & Stokes, 1961).

Recently it has been shown that thallium-201 scintigrams and pyrophosphate scans can detect perfusion defects or cell necrosis in the myocardium in patients with systemic sclerosis (Alexander *et al.*, 1981; Duska *et al.*, 1982). Follansbee *et al.* (1984) studied 23 patients (6, 23%, had clinical evidences of cardiac

involvement) and found that 20 patients (77%) had abnormal thallium redistribution scan. In the present study first pass nuclear ventriculography revealed diffuse wall motion abnormalities in 7/23 patients (30%). Previous studies, both in normal volunteers with a wide age range (Port *et al.*, 1980) and in patients with abnormal exercise test but normal coronary arteries (Berger *et al.*, 1981) have shown a normal left ventricular ejection fraction and wall motion. Given the good agreement between radionuclide and contrast angiography (Dymond *et al.*, 1979) it is unlikely that the wall motion abnormalities detected in 30% of the patients in this study was due to an error in the method. This suggests a generalized distribution of the fibrotic lesions in the ventricular myocardium as described in histopathological studies (D'Angelo *et al.*, 1969; Bulkley *et al.*, 1976; Botstein & LeRoy, 1981). The presence of fibrosis is not necessarily due to coronary artery disease because in most post-mortem studies these lesions were not associated with coronary artery involvement (Bulkley *et al.*, 1976; Oram & Stokes, 1961; Follansbee *et al.*, 1984). The possibility of an ischaemic process in our patients who showed abnormal wall motion cannot be ruled out completely, but with one exception all these patients had a normal electrocardiogram (Table IV) and had no symptoms suggestive of ischaemia. Furthermore, in all the 7 patients there was diffuse rather than localized wall motion abnormalities. Nuclear angiography may therefore be a useful non-invasive test for detection of early myocardial involvement. In future studies the value of provocative manoeuvres such as exercise, cold pressor test should also be evaluated (Alexander *et al.*, 1981; Montanes *et al.*, 1982; Follansbee, 1984).

The 12-lead electrocardiogram revealed a partial and complete RBBB pattern in 18% of this group of patients while 1.4% was estimated in normal population (Ostrander *et al.*, 1965). No other electrocardiographic abnormalities could be found. Escudero & McDewitt (1958) demonstrated that 75% of patients with visceral involvement had abnormal surface electrocardiograms; mainly P wave notching, which was

not observed in this series. The frequency of supraventricular and ventricular arrhythmias on the 24 hour ambulatory electrocardiogram in this series was relatively lower than others (Clements *et al.*, 1981; Ridolfi *et al.*, 1976) and did not differ from the spectrum of arrhythmias encountered among healthy middle-aged populations (Clarke *et al.*, 1976; Verbaan *et al.*, 1978) except for the relatively higher frequency of sinus arrhythmia. The difference between our results and those from other series may be due to patient selection since there was a high proportion of patients with clinical evidence of cardiac involvement in the other series (Clements *et al.*, 1981; Ridolfi *et al.*, 1976).

Many pathological studies (James, 1974; Roberts & Cabeen, 1980; Clements *et al.*, 1981; Lev *et al.*, 1976) have shown a variable degree of sclerosis in the conduction system without any correlation with the electrocardiogram and arrhythmia pattern. It has been suggested that these lesions are probably a part of the diffuse myocardial involvement (Botstein & LeRoy, 1981; Clements *et al.*, 1981; Ridolfi *et al.*, 1976); although focal changes in the specialized conduction tissue have been described (Roberts & Cabeen, 1980). In this study there was no correlation between the electrocardiographic findings and either echocardiographic or nuclear angiographic data. In one series 70% of patients had abnormal findings during electrophysiological study and functional abnormalities of the sinoatrial and atrioventricular nodes were frequently encountered in these patients despite normal surface electrocardiograms (Clements *et al.*, 1981; Ridolfi *et al.*, 1976). The high incidence of RBBB in this series may suggest sclerotic involvement of the conducting tissue. This may have prognostic importance, because there have been reports of sudden death

in systemic sclerosis patients with conducting tissue involvement (James, 1974; Roberts & Cabeen, 1980).

Pericardial involvement is relatively common in systemic sclerosis. Seventy-two per cent of cases have shown some kind of acute or chronic fibrinous pericardial change at post-mortem (D'Angelo *et al.*, 1969; Bjerregaard, 1983; McWhorter & LeRoy, 1974). Such pericardial involvement has usually been clinically silent. Echocardiographic evidence of pericardial thickening was found in 50% of this group and 2 patients (7%) had additional small pericardial effusions. This is significantly higher than the incidence of echocardiographically diagnosed pericardial thickening in a general hospital (173 of 9000 echocardiograms examined; Schnittger *et al.*, 1978). Smith *et al.* (1979) found that 41% of unselected patients with progressive systemic sclerosis had pericardial effusions, but 32% of these patients had signs and symptoms of pericardial effusions. Echocardiography appears useful in the assessment of early pericardial involvement in these patients.

It is obvious from this study that nuclear angiography, 12-lead electrocardiography, echocardiography and 24 hour ambulatory electrocardiography are useful tools for discovering early cardiac involvement in patients with systemic sclerosis. The prognostic value of these investigations is still unclear and further long-term evaluation of these findings is necessary.

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