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Non-invasive evaluation of long-term cardiac effects of captopril in systemic sclerosis

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Abstract. Kazzam E, Caidahl K, Hällgren R, Gustafsson R, Waldenström A (Department of Internal Medicine, University Hospital, Uppsala, and Department of Clinical Physiology, Sahlgren's Hospital, Gothenburg, Sweden). Non-invasive evaluation of long-term cardiac effects of captopril in systemic sclerosis. *Journal of Internal Medicine* 1991; 230: 203–212.

Impairment of left ventricular (LV) function has previously been reported in patients with systemic sclerosis (SScl). An intermittent vasospastic process in the mycocardium may contribute to the development of myocardial dysfunction. Vasodilators may therefore be potentially useful in the treatment of cardiac dysfunction in patients with SScl. This study was designed to evaluate the long-term effects of captopril on the myocardial function of patients with SScl. Twenty-two patients with SScl (15 patients with diffuse scleroderma and 7 patients with CREST syndrome, i.e. calcinosis, Raynaud's phenomenon, oesophageal hypomotility, sclerodactyly, telangiectasia) were investigated by means of Doppler and echophonocardiography before and after treatment with captopril (1.3 mg kg^{-1} body weight d^{-1}) for 11–15 months. There were no significant differences in heart rate, systolic and diastolic blood pressure, end-systolic blood pressure, total peripheral resistance or LV diameters before or after treatment. However, captopril treatment exerted significant effects on LV function: the pre-ejection period (PEP) and the ratio of pre-ejection period to LV ejection time decreased significantly ($P < 0.05$). Mitral E-point septal separation decreased significantly ($P < 0.01$), even after adjustment for LV end-diastolic diameter ($P < 0.01$). The ejection fraction increased significantly ($P < 0.05$), and the isovolumic relaxation time decreased ($P < 0.01$). The left atrial emptying index increased ($P < 0.01$). The Doppler peak late to early ventricular filling velocity decreased ($P < 0.05$), and the isovolumic index was also reduced ($P < 0.05$). We conclude that both systolic and diastolic LV function indices improved in patients with SScl after captopril treatment for a mean period of 1 year. The effects of captopril might be due to vasodilation of the myocardial vessels and/or a direct effect on the renin-angiotensin system of the heart.

Keywords: apexcardiogram, captopril, diastolic function, Doppler echocardiography, left ventricle, systemic sclerosis, systolic function.

Introduction

Systemic sclerosis is a multisystemic connective tissue disease characterized by inflammatory and fibrotic changes in the skin. Visceral involvement is also well recognized, particularly that affecting the lungs, heart, kidneys and gastrointestinal tract [1]. Since it was initially reported by Weiss in 1943 [2], cardiac involvement has been the subject of much interest. The signs and symptoms of myocardial disease in SScl include chest pain, dyspnoea, congestive heart failure and sudden death [3–5]. However, reports on the frequency and severity of cardiac involvement in SScl have produced variable results [3–8].

Recently, we have shown that patients with SScl often suffer from diastolic and systolic left ventricular

(LV) dysfunction, including increased LV wall thickness, impaired early filling properties, and decreased distensibility, as well as reduced contractility and rate of LV emptying [9–11]. Although fibrosis is seen in up to 50% of patients at autopsy, the exact pathogenic mechanisms of the myocardial lesions associated with SScl are still only poorly understood [2].

Currently there is no standard treatment for SScl. The treatments that are in use are solely for the treatment of symptoms associated with the disease [7]. We recently reported a vasospastic component as a possible cause of the cardiac abnormality in SScl [12]. Captopril—an orally active angiotensin-converting-enzyme (ACE) inhibitor—is reported to be effective in the treatment of renal crisis in SScl [13]. Since a renal vasospasm has been proposed as a cause of the renal crisis in this disease, we postulated that captopril may have beneficial effects on myocardial function as well. To date, there have been no reports on the cardiac effects of captopril in this disease. The present study was designed to evaluate the long-term effects of captopril on LV function in patients with SScl.

Subjects and methods

Subjects

Twenty-two consecutive patients (12 men and 10 women), aged 27–77 years (mean age 56 years), with SScl (15 patients with diffuse scleroderma and 7 patients with CREST syndrome) diagnosed according to American Rheumatism Association (ARA) criteria [14] were studied. The patients were referred from the Uppsala region to the University Hospital of Uppsala. Their disease had been recognized for 0.5–23 years, with a mean duration of 6 years. The clinical characteristics of the patients are shown in Table 1.

All patients were hospitalized and their cardiac function was evaluated clinically. Before cardiac investigations patients were treated according to the criteria shown in Table 1. All medication was withdrawn at least 4 d before non-invasive cardiac examinations. Thereafter, the patients were put on their previous medication, if any. Treatment was initiated with a low dose of captopril for the first 3 d, and the dose was gradually increased during the following 2 weeks. The total average daily dose ($\pm$SEM) was 1.3 ± 0.06 mg kg^{-1} body weight. Blood pressure was assessed prior to and during treatment. Each patient was investigated prior to the treatment and after 11–15 months, when all treatment was again stopped 4 d before cardiac investigation. None of the patients developed any recognized side-effects during treatment.

Methods

A standard 12-lead resting electrocardiogram (ECG), pulse curves and a phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden), as described previously [15]. Briefly, 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 recordings were obtained similarly, but with the patient lying in the left lateral position.

Blood pressure was recorded at rest in the supine position 30 min after the pulse recordings and immediately before the M-mode recordings. The standard sphygmomanometer technique was applied, and the mean value of three readings was used.

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. Two-dimensional guided M-mode echocardiograms 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.

A Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record the mitral flow spectrum as described previously [11].

Measurements

All measuring points were agreed upon by two observers (EK and KC). One investigator (EK) made all interpretations after the recordings had been coded and randomly mixed by another investigator. Only beats of acceptable or good quality were used for measurements.

From M-mode echocardiographic recordings, the following measurements were made on three beats (leading edge to leading edge method) according to the recommendations of the American Society of

Table 1. Clinical data for the patients with systemic sclerosis

Patient no.	Sex (M/F) and age (years)	Disease duration (years)	Systemic sclerosis score (0–54)	SBP/DBP (mmHg)	TPR (dynes s^{-1} cm^{-5})	ESR (mm h^{-1})	FEV_1 (% of predicted value)	Serum creatinine (μmol l^{-1})	Medication
1	M68	12	36*	140/73	1452	85	89	72	—
2	M54	1	29*	95/65	2284	8	73	79	Nifedipine
3	M68	5	34*	125/76	1714	44	45	107	Frusemide
4	M77	0.5	41*	125/77	1832	36	91	97	—
5	F43	2	30†	132/80	1191	13	51	85	Nifedipine
6	F48	0.5	34†	120/75	593	95	72	90	—
7	F65	7	27*	123/73	1500	8	93	87	—
8	F67	23	31†	127/70	1126	95	90	68	—
9	F66	5	25*	130/90	2085	22	76	59	Hydrochlorothiazide
10	F42	0.5	21†	165/80	—	20	100	64	Verapamil
11	M59	20	28†	122/61	1358	20	57	79	—
12	F65	0.5	16*	103/64	1829	22	66	76	—
13	M59	3	24*	127/79	—	7	80	67	—
14	M50	0.5	8†	138/81	1275	60	56	71	—
15	M46	4	21*	160/70	1177	56	91	50	—
16	F70	8	34*	157/110	1393	20	90	79	—
17	M39	1	11*	165/80	1863	8	75	91	Digoxin
18	M48	1	25*	125/75	1306	7	93	80	—
19	F73	1	37*	133/90	920	4	63	78	—
20	M27	7	10*	125/75	2123	46	121	110	—
21	M43	10	31*	139/88	1887	10	109	75	—
22	F51	1	11†	110/73	846	18	66	81	—

SBP = systolic blood pressure, DBP = diastolic blood pressure, TPR = total peripheral resistance, ESR = erythrocyte sedimentation rate, FEV_1 = forced expiratory volume during 1 s expressed as a percentage of predicted value.
*Patients with diffuse scleroderma.
†Patients with CREST syndrome.

Echocardiography [16], and the mean value was used in subsequent calculations. The LV internal diameters at end-diastole and systole, the interventricular septal thickness and the 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 the amplitudes from pulse tracings, were measured by means of a digitizing table-minicomputer system. Fractional shortening was defined as the difference between the LV diastolic and systolic dimensions, divided by the diastolic dimensions. The ejection fraction was calculated as described previously [10]. The mean velocity of circumferential fibre shortening was calculated as the fractional shortening divided by the LV ejection time. Mitral E-point to septal separation was defined as the vertical distance (mean value of five beats) between the E-point of the anterior mitral leaflet and the ventricular septum [17]. E-point to septal separation was adjusted to the end-diastolic LV dimension. LV meridional end-systolic wall stress (10^3 dynes cm^{-2}) was estimated as end-systolic wall stress = $(1.332 \times ESBP \times D)/[4\,h \times (1 + h/D)]$, where D represents the LV end-systolic dimension, h is the mean value of the septal and posterior wall end-systolic thicknesses, and ESBP is the end-systolic blood pressure [18]. End-systolic blood pressure was obtained by linear interpolation to the height of the dicrotic notch of the carotid curve, after assigning systolic and diastolic blood pressures to the peak and nadir of the curve [19]. The left atrial emptying index was obtained from the posterior aortic wall motion as an estimate of early LV filling properties [9]. The atrial emptying index was also corrected for heart rate (AEI%).

From the Doppler mitral spectral flow, the peak velocity of early LV filling (peak E) and the peak velocity of late LV filling (peak A) were measured in five beats, and the mean values were used. The peak A/E ratio was calculated.

Measurements of pulse curve tracings were performed in five beats, and the mean values were

Table 2. Characteristics of patients with systemic sclerosis before and after treatment

Parameter	Before treatment	After treatment	*P*-value
Height (cm)	170.2±11	170.1±10	NS
Weight (kg)	64.1±11	64.5±11	NS
Body surface area (m^2)	1.74±0.2	1.75±0.2	NS
Body mass index (kg m^{-2})	36.6±3.1	36.8±3.2	NS
Heart rate (beats min^{-1})	68±12	72±11	NS
Systolic blood pressure (mmHg)	131±21	126±18	NS
Diastolic blood pressure (mmHg)	77±12	75±14	NS
Total peripheral resistance (dynes s^{-1} cm^{-5})	2970±843	2693±1129	NS

Mean values±SD are shown.

Table 3. LV systolic function in patients with systemic sclerosis before and after treatment with captopril

Parameter	Before treatment	After treatment	*P*-value
PEP (ms)	111.3±20	94.2±18	0.05
PEP/LVET ratio	0.37±0.07	0.32±0.08	0.05
EPSS (mm)	7.5±2.9	5.1±2.8	0.01
EPSS/EDD (mm)	0.158±0.06	0.112±0.06	0.01
Ejection fraction	0.70±0.10	0.74±0.06	0.05
ESWS (10^3 dynes cm^{-2})	52.3±16	44.7±13	NS
Vfc	1.11±0.23	1.26±0.22	0.05
Fractional shortening	0.34±0.07	0.37±0.05	0.05

PEP = pre-ejection period, LVET = left ventricular ejection time, EPSS = mitral E-point septal separation, EDD = end-diastolic diameter, ESWS = end-systolic wall stress, Vfc = velocity of circumferential fibre shortening.
Mean values±SD are shown.

used. The LV ejection time, the pre-ejection period and the relaxation time index were measured from simultaneous recordings of the electrocardiographic lead II, the phonocardiogram and the carotid pulse tracing or apexcardiogram [15]. The isovolumic index was defined as [(R-mitral valve opening-LV ejection time)/LV ejection time] × 100 [20].

Total peripheral resistance was calculated according to the following formula: total peripheral resistance = mean arterial blood pressure × 1.33 (60/Doppler cardiac output).

Clinical studies

Lung function was estimated by the measurement of forced expiratory volume during 1 s; the lower normal limit in our laboratory is 80% of the predicted value. The erythrocyte sedimentation rate was measured after 1 h (Westergren), and serum creatinine levels were measured at the department of Clinical Chemistry.

Raynaud's phenomenon score was based on a scale of 0–4, where 0 denotes no signs of the phenomenon, and 4 denotes the most severe form, with cyanotic fingers even at 20 °C.

The severity of skin lesions was assessed by a simple scoring system; skin thickening was estimated at 18 anatomical sites on a scale of 0–3, where 0 denotes normal skin and 3 denotes the most severe thickening and induration of the skin. The maximum score was therefore 54.

Statistical analyses

Data are presented as mean values±SD of the mean. A paired two-sided *t*-test was used to compare the results before and after treatment. A *P*-value of < 0.05 was regarded as statistically significant. Linear correlation tests were used as indicated.

Table 4. LV diastolic function in patients with systemic sclerosis before and after treatment with captopril

Parameter	Before treatment	After treatment	*P*-value
Heart rate (beats min^{-1})	67±8.6	71±15.3	NS
A2-O (ms)	150±23.4	139±14.4	0.01
LV EDD (mm)	47.2±4.9	47.3±6.2	NS
Septal thickness (mm)	12.0±3.1	12.0±2.3	NS
Posterior wall thickness (mm)	10.1±1.9	9.8±2.0	NS
LV mass (g)	195±64	195±66	NS
LV mass index (g m^{-2})	111±34	111±35	NS
Left atrial diameter (mm)	38.7±6.1	37.9±9.9	NS
Left atrial index (mm m^{-2})	22.4±4.5	22.8±6.1	NS
AEI	0.67±0.16	0.78±0.24	0.01
AEI%	79.3±14	92.3±28	0.01
Doppler A/E	1.14±0.48	0.97±0.44	0.05

A2-O = time from A2 to the apexcardiographic O-point, LV = left ventricular, A/E = the ratio of the late to early peak velocity, AEI = atrial emptying index, AEI% = heart rate-corrected AEI.
Mean values±SD are shown.

Results

Effect of captopril on haemodynamic data

Weight, body surface area and body mass index did not change significantly during treatment. Captopril induced no significant changes in heart rate, systolic and diastolic blood pressure, end-systolic blood pressure or total peripheral resistance (Table 2).

Effect of captopril on left ventricular systolic function

The ratio of pre-ejection period to LV ejection time decreased significantly during captopril treatment ($P < 0.05$), indicating an improvement in LV contractility (Table 3). E-point to septal separation was significantly decreased after treatment ($P < 0.01$), even after adjustments for LV end-diastolic diameter ($P < 0.01$) had been made. There was a significant correlation between E-point to septal separation and pre-ejection period/LV ejection time ($P < 0.001$), as well as isovolumic index ($P < 0.01$). The ejection phase indices, namely ejection fraction, fractional shortening and velocity of circumferential fibre shortening, were all significantly increased ($P < 0.05$).

Effect of captopril on left ventricular diastolic function

There were no significant changes in left atrial diameter, LV dimension or wall thickness (Table 4). Thus LV mass was not altered by captopril treatment. Despite this, diastolic function improved. The relaxation period, measured from the apexcardiogram, was shortened ($P < 0.01$). Early filling, measured by the atrial emptying index, was significantly increased ($P < 0.01$). The Doppler echocardiographic A/E ratio decreased ($P < 0.05$), indicating an improvement in LV distensibility.

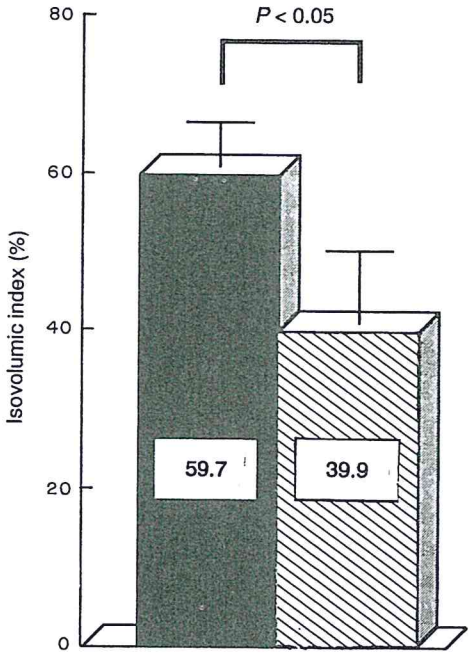

Fig. 1. Effect of captopril treatment on isovolumic index: (■) = before treatment; (▨) = after treatment.

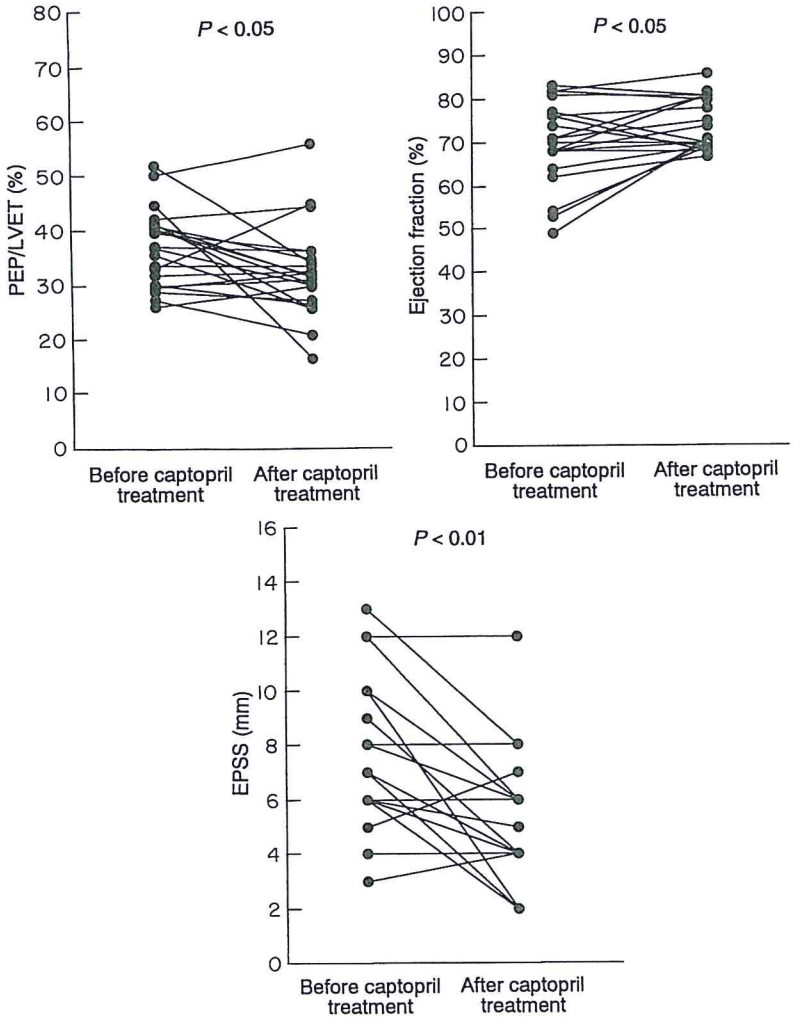

Fig. 2. Effects of captopril treatment on LV systolic function.

Effect of captopril on isovolumic index

The isovolumic index (Fig. 1) decreased significantly ($P < 0.01$) after captopril treatment, from 59.7 to 39.9%. No significant correlation was found between isovolumic index and age, heart rate, systolic blood pressure, diastolic pressure or total peripheral resistance. However significant correlations were detected between the isovolumic index and the ratio of pre-ejection period to LV ejection time ($P < 0.001$), the ejection fraction ($P < 0.01$), the mitral E-point to septal separation ($P < 0.01$), and the atrial emptying index % ($P < 0.01$).

Individual data

During captopril treatment, the ratio of pre-ejection period to LV ejection time decreased in 64% of patients and increased in 36% of patients. The ejection fraction increased in 60% of patients, decreased in 25% of patients and remained unchanged in 15% of patients. The mitral E-point to septal separation decreased in 63% of patients, increased in 11% of patients and remained unchanged in 15% of patients. The isovolumic relaxation period (A2-O) was reduced in 63% of patients, prolonged in 32% of patients and remained unchanged in 5% of patients. The atrial emptying index increased in 90% and decreased in 10% of patients. The Doppler A/E ratio decreased in 70% of patients, increased in 18% of patients and remained unchanged in 6% of patients.

Systolic function (Fig. 2) (evaluated by pre-ejection period to LV ejection time, ejection fraction and E-point to septal separation) improved in 62% of patients. Of these, 64% showed improvement by one

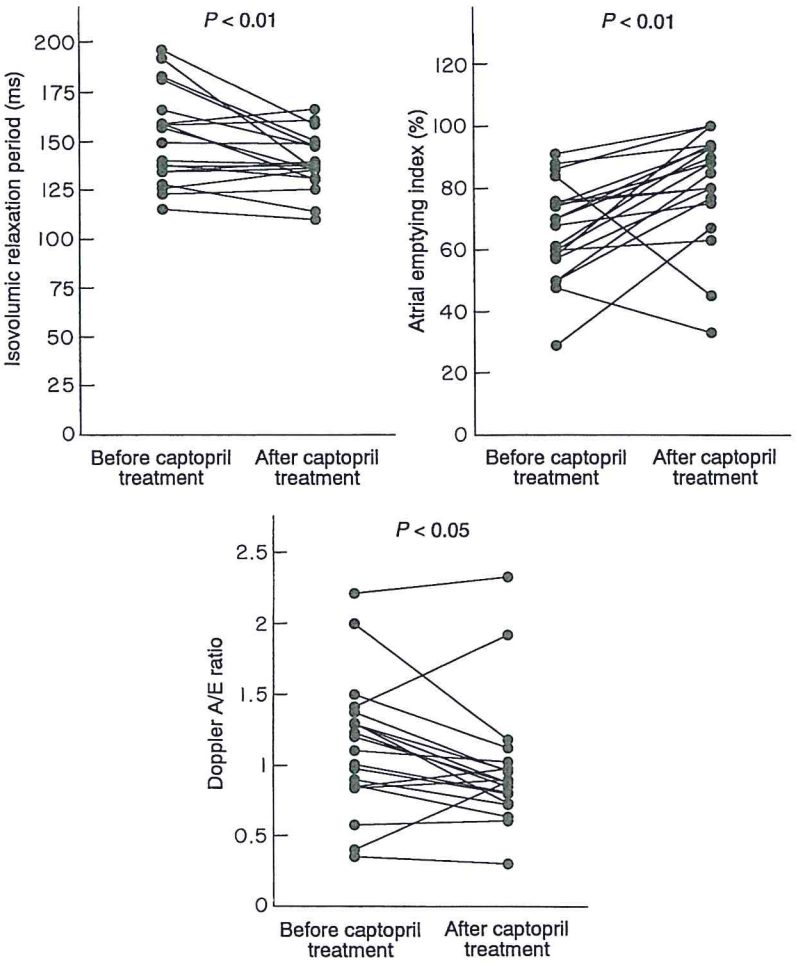

Fig. 3. Effects of captopril treatment on LV diastolic function.

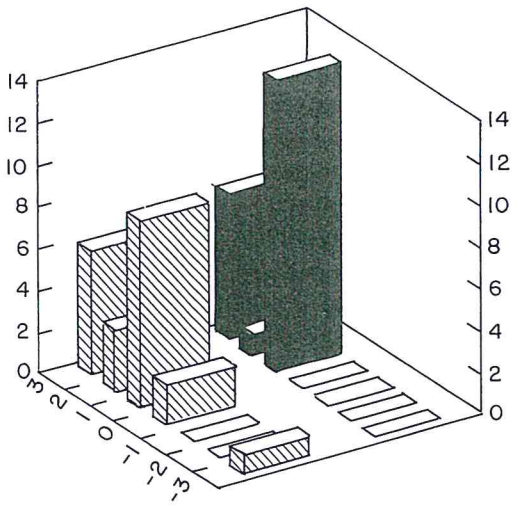

Fig. 4. The cardiac improvement after captopril treatment as evaluated by systolic (■) and diastolic (▨) function.

systolic variable, 4% by two variables and 32% by three variables. Diastolic function (Fig. 3) (evaluated by isovolumic relaxation period (A2-O), atrial emptying index and A/E) was improved in 74% of patients. Of these, 43% showed improvement by one diastolic variable, 14% by two variables and 28% by three variables. One patient showed deterioration in all three diastolic variables.

We also calculated the number of patients who showed an improvement or deterioration in the systolic variables (Fig. 2) and diastolic variables (Fig. 3). Each variable was counted as one score point. Thus improvement in one variable, deterioration in one variable, and no change in the third variable gave a total score of zero. The results are shown in Fig. 4.

Discussion

The present prospective study of the long-term effects of captopril clearly demonstrated an improvement in both systolic and diastolic LV function.

Systolic time intervals, as the pre-ejection period and the ratio of pre-ejection period to LV ejection time, are abnormal in patients with SScl [10]. These time intervals improved significantly after captopril treatment. Systolic time intervals have been shown to be a sensitive method for revealing the effect of vasodilators on ventricular performance in chronic heart failure [21], and are even more effective than ejection fraction [22]. The improvement in systolic function was further evident and characterized by a reduction in E-point to septal separation and increased fractional shortening, despite the fact that there were no changes in preload (end-diastolic diameter) or afterload (end-systolic blood pressure, total peripheral resistance, end-systolic wall stress). E-point to septal separation and E-point to septal separation adjusted to the end-diastolic diameter are good indicators of LV performance. They provide a useful reflection of overall LV performance, and we used these parameters because they are easily recorded and reproducible, they are not dependent on a mathematical formula or geometric assumptions, and they are unaffected by heart rate or rhythm [17, 23]. It has been shown that isovolumic index and E-point to septal separation represent a sensitive non-invasive combination for the evaluation of LV performance [20].

The relaxation time of apexcardiogram (A2-O) was significantly reduced after captopril treatment. The A2-O- interval is a valuable measure of LV relaxation [24], and an increase in this interval indicates a reduced rate of fall in LV pressure in early diastole, reflecting diastolic dysfunction [15]. Myocardial fibrosis and a reduced coronary vasodilatory capacity secondary to ischaemia are possible mechanisms that may impair relaxation and prolong the A2-O- interval [25]. The atrial emptying index was also significantly increased after captopril treatment, indicating an improvement in early filling properties of the LV. The atrial emptying index has been shown to be of value in the assessment of LV diastolic function in SScl [9], hypertension and congestive heart failure [26, 27]. The Doppler echocardiographic A/E ratio was significantly reduced during captopril treatment, indicating an improvement in LV distensibility. The isovolumic index is a sensitive indicator of LV dysfunction in cardiomyopathy and coronary heart disease [20]. It is easily recorded, and is not related to heart rate, age, blood pressure or total peripheral resistance. The isovolumic index is a combined measurement of both systolic and diastolic function; thus the significant improvement in LV function estimated by the isovolumic index during captopril treatment of patients with SScl supports our other findings of enhanced LV contractility after captopril treatment.

The usefulness of captopril in the treatment of heart failure and hypertension has been well documented [28–30]. The mechanism underlying functional cardiac improvement has been attributed to reduced vascular resistance, resulting in a decreased afterload and an increased cardiac output [28]. This open study in SScl has shown that LV contractility, as well as a prolonged LV isovolumic relaxation time, impaired LV filling and distensibility may also be favourably influenced by the long-term administration of captopril. Captopril induced no significant changes in the LV end-diastolic diameter, end-diastolic volume, blood pressure, total peripheral resistance or end-systolic wall stress. However, total peripheral resistance decreased by 9.3% and end-systolic wall stress decreased by 14.5%. Thus some effects of a non-significant decrease in afterload on functional variables could not be excluded.

Focal myocardial fibrosis, reported by several authors [31–33], may be the reason for the development of myocardial dysfunction in systemic sclerosis. However, even patients with systemic sclerosis who die suddenly appear to have conspicuously normal extramural coronary arteries at autopsy [34, 35]. Focal myocardial lesions bear no relation to specific extramural vasculature [31], and myocardial necrosis occurs with widely patent intramural and extramural coronary arteries, suggesting that the microcirculation is abnormal [35, 4, 8]. Although patients with arrhythmias and conduction disturbances who die suddenly have been found to have their sinus node artery and AV-node artery affected [34], an autopsy study of 52 patients has shown intramural coronary arteries to be generally normal histologically, and micro-angiograms in 12 patients to be free from abnormalities [31]. It has been suggested that vasospasm or myocardial Raynaud's phenomenon are responsible for the myocardial necrosis observed in systemic sclerosis [35, 4], and we were recently able to substantiate this hypothesis by demonstrating

in the present study group reversible myocardial perfusion defects induced by cold provocation [12]. Since, in the patient with the largest myocardial perfusion defects, arteriography revealed 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, for ethical reasons we could not have conducted comparative studies in the control group.

The local presence of a renin-angiotensin system has been reported in many organs, including blood vessels and the heart, and it may affect local tissue function [36, 37]. The improvement in LV function due to captopril treatment is unlikely to be secondary to the effects on heart rate or blood pressure, since these variables did not change significantly. Thus it is more likely that captopril exerted its effect by vasodilation of the myocardial vessels, decreasing the circulation angiotensin II level, or by a direct influence on the local angiotensin system in the heart [30], or by other mechanisms that affect the myocardium. Since vascular spasm of the myocardial vessels is commonly observed in patients with SScl [12], a possible explanation for the captopril effect may be vasodilation at the microcirculatory level, leading to an improvement in myocardial perfusion.

We conclude that both systolic and diastolic cardiac abnormalities in patients with SScl can be reversed by treatment with captopril. A spontaneous remission of the cardiac abnormalities in SScl appears to be a remote possibility, due to the progressive nature of the disease. The observed cardiac effects of captopril, and the question of whether captopril exerts a direct effect on the myocardial vessels, have to be confirmed in a prospective randomized double-blind study involving pathoanatomical evaluation of myocardial biopsies.

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