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Cardiac and Pulmonary Functional Responses to Angiotensin Converting Enzyme Inhibitors in Scleroderma Patients

HUSSEIN BADRAWY, M.D.; ABD EL-GALIL MOSTAFA, M.D.; GAAFAR M. RAGAB, M.D.; OMAIMA EL-HENNAWY, M.D.; HATIM M. ABDEL-RAHMAN, M.D.; HEDEYA H. EL-IBRACHY, M.D.; MERVAT M. LABIB, M.D. and ASHRAF HATEM, M.D.

The Departments of Internal Medicine and Chest, Faculty of Medicine, Cairo University

Abstract

Eight patients fulfilling the clinical criteria for diagnosis of scleroderma were subjected to clinical evaluation, laboratory investigations, plain chest X-ray, ECG, basal pulmonary function tests (PFTs) and basal echocardiographic assessment and Doppler (ECA). Captopril 75 mg/day was given for one week and then PFTs and ECA were repeated. 62.5% of patients had pulmonary hypertension, 25% pulmonary regurge, 37.5% mitral regurge, and 62.5% tricuspid regurge. There was a pericardial effusion in 25% of cases. There was no statistically significant change of left ventricular internal dimensions, volume and mass before and after captopril. Velocity of circumferential shortening, posterior wall excursion, velocity of the posterior wall and its normalised value showed statistically significant increase following captopril intake. There was also a statistically significant drop of pre-ejection period after captopril. There was a statistically significant imporvement of mitral E/A. There was a statistically significant rise of acceleration time and its ratio to ejection time after captopril intake in both aortic and pulmonary flow. Spirometric studies before and after captopril showed no statistically significant change of all parameters except FEV 25-75 which increased. We thus concluded that in patients with systemic sclerosis, captopril significantly improved left ventricular systolic and diastolic functions, pulmonary and aortic resistance and blood flow. It had no effect on pulmonary functions.

Introduction

SCLERODERMA is a severe systemic collagen vascular disease of unknown cause characterized by marked vascular and connective tissue abnormalities affecting skin, gastrointestinal tract, lungs, heart and kidneys [1].

Systemic sclerosis (SS) may be accompanied by pulmonary hypertension which may result from pulmonary artery vasculitis, pulmonary artery vasoconstriction of hypoxic origin during diffuse interstitial fibrosis, a thromboembolic mechanism or a vasomotor phenomenon [2].

Cardiac involvement in systemic sclerosis accounts much for disease mortality and takes the form of dilated or restrictive cardiomyopathy [3]. Echocardiographic studies in SS showed diastolic and systolic left ventricular dysfunction [4].

Captopril is an angiotensin converting enzyme inhibitor known to reduce ventricular pre and after load and has the potential to reduce pulmonary hypertension [5].

The aims of the present study are:

1. To study left ventricular function and pulmonary blood flow before and after angiotensin converting enzyme inhibition in patients with systemic sclerosis.

2. to study the pulmonary functions before and after angiotensin converting enzyme inhibition in patients with systemic sclerosis.

Material and Methods

Eight cases were selected for the study. They were normotensive. They fulfilled clinical and laboratory criteria for diagnosis of scleroderma with their age ranging from 13-50 years. Each patient was subjected to the following in order:

a) Clinical assessment with skin scoring according to Rodnan skin score system [6].

b) ECG.

c) Plain chest X-ray.

d) Respiratory function tests

Full spirometric study using sensor Medics 2200 Spirometry Apparatus for performing flow volume loop and single breath carbon monoxide diffusion capacity (DLCO) test. The test was repeated three times and the best result was chosen for each of the following parameters:

Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC and peak expiratory flow rate (PEFR).

e) M-mode, two dimensional (2D) echocardiographic assessment and Doppler study using Acuson Computed Ultrasound System 128xp/10, Mountion view USA model. The probes used were 2.5 and 3.5 mega Hertz. Left and right ventricular, left atrial, aorta and pulmonary artery measurements and left ventricular contractility indices were assessed. Doppler was

used to record aortic, pulmonary and mitral E/A flow measurements.

f) One week of therapy with oral captopril 75mg/day in three divided doses after which patient was subjected to a second assessment of respiratory function tests and echocardiography.

Statistical analysis was done using an IBM compatible computer system. The analysis was done by means of statistical software package (Statview). The Student t-test could not be used because of the small number of our sample. This necessitated the use of Wilcoxon Signed Rank test [7].

Results

The study was conducted on eight SS patients. All cases were females. their age renged from 13-50 years with a mean of 30.6±15.9. All cases had woody skin with Rodnan skin score ranging from 28 to 82 with a mean of 48.1±20.7.

The duration of illness ranged from 2 to 35 years with a mean of 11.9+10.8 years. Reynaud's phenomenon was present in all cases, hair loss in 2 cases (25%). Superficial skin ulcers in 6 cases (75%). Joint pain in 6 cases (75%), joint tenderness in 3 cases (37.5%) and dysphagia in 6 cases (75%), dyspnoea in one case (12.5%) but there was no orthopnoea in any of the cases. History of lower limb edema was present in 2 cases (25%). There was clinical evidence of right ventricular enlargement in 3 cases (37.5%). All patients gave no history of rheumatic fever. All patients were subjected to a bed side ECG which revealed right bundle branch block in one case (12.5%), P-pulmonale in 2 cases (37.5%) and ECG evidence of left ventricular hypertrophy in one case (12.5%).

All patients were subjected to plain chest X-ray, postro-anterior and lateral views, which revealed cardiac enlargement in 4 cases (50%), pulmonary artery dilatation in 5 cases (62.5%), and abnormalities in the lung fields in 3 cases, in the form of increased interstitial markings in one, prominent bronchovascular marking in another and bilateral hilar congestion in the third.

The results of echocardiographic, Doppler and spirometeric values were shown in tables I-VIII as well as their statistical analyses.

Discussion

Basal echocardiographic findings in our study showed increase in the left ventricular posterior wall thickness and that of the interventricular septum than the normal range (table II). The same findings were reported by others [8,9] in patients with SS without systemic hypertension and this hypertrophy was attributed to collagen deposition between the myofibrils.

Table (I): Echocardiographic Valvular, Pericardial & Cardiac Chamber Findings In Scleroderma Patients.

Parameter	Case I	Case II	Case III	Case IV	Case V	Case VI	Case VII	Xase VIII
Pulmonary Valve	Pulmonary Hypertension	Pulmonary Hypertension	Pulmonary Hypertension + Pulmonary Regurge	-	-	Pulmonary Hypertension	Pulmonary Hypertension + Pulmonary Regurge	-
Mitral Valve	Thickened Mitral Leaflets	Mitral Leaflets	Mitral Regurge	-	-	Mitral Valve Prolapse	-	-
Tricuspid Valve	Tricuspid Regurge	Tricuspid Regurge	Tricuspid Regurge	-	-	Tricuspid Regurge	Tricuspid Regurge	-
Pericardial Effusion	-	+	+	-	-	–	-	-
Left Atrium	Dilated	-	–	-	-			
Left Ventricle	-	–	Hypertrophy	–	–	Dilated -	– -	- -

Table (II): Statistical Comparison of Left Ventricular Findings in Scleroderma Before and After Captopril.

	Before Captopril					After Captopril					z	p	Comment
Prarameter	Cases No.	Min.	Max.	Mean	S.D.	Cases No.	Min.	Max.	Mean	S.D.	Wilcoxon Rank Test		
LVID - d	8	3.8	5.36	4.42	0.5	8	3.63	5.06	4.21	0.54	0.42	> 0.1	N. S.
LVID - s	8	2.25	3.34	2.76	0.4	8	2.11	3.24	2.62	0.53	0.42	> 0.1	N. S.
LVV - d	8	61.9	138.9	89.99	24.79	8	55.5	121.6	80.75	24.91	0.42	> 0.1	N. S.
LVV - s	8	17.1	45.4	32.31	12.62	8	10.9	42.2	26.66	12.71	0.42	> 0.1	N. S.
LV - mass	8	81	178	119.13	35.71	8	73	178	116.75	37.17	0.42	> 0.1	N. S.
PWT - d	8	0.66	1.13	0.83	0.15	8	0.66	1.02	0.81	0.14	0.42	> 0.1	N. S.
PWT - s	8	0.8	1.71	1.288	0.21	8	1.02	1.8	1.38	0.28	1.12	> 0.1	N. S.
IVS - d	8	0.55	1.34	0.86	0.25	8	0.66	1.41	0.97	0.22	1.12	> 0.1	N. S.
IVS - s	8	0.74	1.71	1.22	0.28	8	0.74	1.76	1.31	0.36	1.12	> 0.1	N. S.

LVIDd: Left ventricular internal dimensions in diastole.
LVIDs: Left ventricular internal dimensions in systole.
LVVd: Left ventricular volume in diastole.
LVVs: Left ventricular internal systole.
LV mass: Left ventricular mass.
PWT.d.: posterior wall thickness in diastole.
PWT.s.: posterior wall thickness in systole.
IVSd, IVSs: interventricular septum in diastole and systole.
N. S. : Not Significant.

Table (III): Statistical Comparison of Right Ventricular Findings in Scleroderma Before and After Captopril.

	Before Captopril					After Captopril					z	p	Comment
Prarameter	Cases No.	Min.	Max.	Mean	S.D.	Cases No.	Min.	Max.	Mean	S.D.	Wilcoxon Rank Test		
RVD - d	8	1.22	2.25	1.76	0.45	8	1.36	2.05	1.68	0.27	0.42	> 0.1	N. S.
RVD - s	8	1.05	1.8	1.34	0.24	8	1.09	1.69	1.31	0.2	0.42	> 0.1	N. S.
RVW - d	8	0.27	1.26	0.54	0.31	8	0.23	0.81	0.42	0.19	0.42	> 0.1	N. S.
RVW - s	8	0.38	1.51	0.75	0.34	8	0.52	0.94	0.69	0.13	1.02	> 0.1	N. S.

RVD-d: Right ventricular internal dimensions in diastole.
RVD-s: Right ventricular internal dimensions in systole.
RVWd: Right ventricular volume in diastole.
RVWs: Right ventricular internal systole.
N. S. : Not Significant.

Table (IV): Statistical Comparison of Left Atrial & Mitral Valve Flow Findings in Scleroderma Before and After Captopril.

	Before Captopril				After Captopril					z	p	Comment
Prarameter	Cases No.	Min.	Max.	Mean	S.D.	Cases No.	Min.	Max.	Mean	S.D.	Wilcoxon Rank Test		
LA	8	2.28	4.88	3.32	0.8	8	2.59	4.38	3.2	0.59	1.12	> 0.1	Not Significant
Mitral E/A	8	0.55	1.57	1.09	0.31	8	0.55	1.9	1.21	0.49	1.68	< 0.05	Significant

LA : Left atrial diameter Mitral E/A: early ventricular filling / late ventricular filling

Table (V): Comparison of Echocardiographic Aortic Findings Before and After Captopril in Scleroderm.

Prarameter	Before Captopril					After Captopril					z	p	Comment
	Cases No.	Min.	Max.	Mean	S.D.	Cases No.	Min.	Max.	Mean	S.D.	Wilcoxon Rank Test		
Ao diameter	8	2.38	3.14	2.7	0.28	8	2.48	3.1	2.78	0.25	1.12	> 0.1	Not Significant
ET	8	0.26	0.328	0.29	0.03	8	0.23	0.343	0.28	0.04	1.12	> 0.1	Not Significant
AT	8	0.06	0.098	0.073	0.014	8	0.05	0.112	0.087	0.025	1.68	< 0.05	Significant
AT/ET	8	0.21	0.32	0.26	0.04	8	0.18	0.42	0.31	0.1	2.1	< 0.05	Significant
PEP	8	0.05	0.094	0.07	0.02	8	0.04	0.066	0.05	0.01	2.5	< 0.1	Significant
PEP/ET	8	0.16	0.361	0.23	0.07	8	0.14	0.246	0.18	0.04	2.5	< 0.1	Significant

Ao diameter : aortic diameter.
ET : ejection time.
AT: acceleration time.
AT / ET: acceleration time / ejection time ratio.
PEP: pre ejection period.

Table (VI): Statistical Comparison of Left Ventricular Contractility Indices in Scleroderma Before and After Cartoril.

	Before Captopril					After Captopril					z	p	Comment
Prarameter	Cases No.	Min.	Max.	Mean	S.D.	Cases No.	Min.	Max.	Mean	S.D.	Wilcoxon Rank Test		
VPW	8	2.8	3.6	3.15	0.43	8	2.9	4.8	3.73	0.59	2.521	< 0.1	Significant
VIVS	8	1.9	2.8	2.36	0.29	8	2.2	3.2	2.84	0.32	2.38	< 0.1	Significant
VPW (norm)	8	0.56	0.8	0.71	0.09	8	0.67	1.06	0.86	0.15	2.38	< 0.1	Significant
VIVS (norm)	8	0.41	0.68	0.54	0.09	8	0.46	0.98	0.73	0.17	2.521	< 0.1	Significant
FS	8	32	49	37.38	6.41	8	20	50	37.88	8.71	0.42	> 0.1	Not Significant
EF	8	54	81	67.13	8.13	8	42	75	67.63	11.96	0.42	> 0.1	Not Significant
VCF (FS / ET)	8	0.85	1.53	1.20	0.2	8	0.66	1.58	1.34	0.32	1.68	< 0.05	Significant
PWE	8	0.8	1.26	1.08	0.16	8	0.91	1.56	1.15	0.22	2.1	< 0.05	Significant
IVSE	8	0.47	0.8	0.67	0.11	8	0.55	0.88	0.71	0.12	0.42	> 0.1	Not Significant

VPW: velocity of posterior wall excursion.
VIVS: velocity of interventricular septal excrursion.
VPW norm: normalised value of VPW.
VIVS norm: normalised value of VIVS.
F.S: fractional shortening %.
E.F: ejection fraction %.
VCF: Velocity of cumferential fiber shorthening.
PWE: posterior wall excurion.
IVSE: interventricular septal excursion.

Table (VII): Statistical Comparison of Pulmonary Artery Flindinges in Scleroderma Before and After Captopril.

Prarameter	Before Captopril				After Captopril					Z Wilcoxon Rank Test	P	Comment
	Cases No.	Min.	Max.	Mean	S.D.	Cases No.	Min.	Max.	Mean	S.D.			
PULM	8	1.96	3.1	2.28	0.36	8	1.82	2.38	2.11	0.22	1.4	> 0.1	Not Significant
PV (max)	8	0.73	1.08	0.91	0.11	8	0.7	0.96	0.82	0.12	1.4	> 0.1	Not Significant
PVTI	8	0.11	0.226	0.19	0.04	8	0.12	0.193	0.17	0.02	1.4	> 0.1	Not Significant
AT	8	0.048	0.15	0.1	0.04	8	0.1	0.16	0.12	0.02	2.1	< 0.05	Significant
ET	8	0.288	0.352	0.33	0.02	8	0.76	0.416	0.34	0.04	1.12	> 0.1	Not Significant
AT/ET	8	0.14	0.457	0.28	0.12	8	0.24	0.476	0.36	0.07	2.1	< 0.1	Significant
Mean Accel.	8	5.4	16.08	10.09	3.97	8	6	8.01	6.99	0.71	0.42	> 0.1	Not Significant

Pulm: pulmonary artery diameter.
PVmax. : maximal pulmonary flow velocity.
PVTI: pulmonary integral area under the curve
AT: acceleration time.
ET: ejection time.
Mean Accel: mean acceleration.

Table (VIII): Statistical Comparison of Pulmonary Vartery Flindinges in Acleroderma Before and After Captopril.

	Before Captopril					After Captopril					z	p	Comment
Prarameter	Cases No.	Min.	Max.	Mean	S.D.	Cases No.	Min.	Max.	Mean	S.D.	Wilcoxon Rank Test		
FVC	7	42	92	61.86	17.3	7	40	73	57.29	10.81	0.169	> 0.1	Not Significant
FEVI	6	36	75	57.5	13.13	6	37	72	57.67	12.94	1.572	> 0.1	Not Significant
FEVI / FVC	6	74	103	87.33	10.35	6	80	97	87.5	6.56	0.943	> 0.1	Not Significant
FEV 25-75	7	20	94	61.29	25.97	7	22	100	67.71	29.4	1.859	< 0.05	Significant
PEF	7	24	111	62.57	27.15	7	27	82	62.28	17.49	0.859	> 0.1	Not Significant
DLCO	7	30	91	64.14	24.7	7	23	155	64.57	44.24	0.676	> 0.1	Not Significant
VA	7	1.7	5.62	3.19	1.34	7	2.12	6.00	3.14	1.34	0.676	> 0.1	Not Significant
DLCO / VA.	7	38	122	75.86	26.31	7	29	122	77.71	31.4	0.676	> 0.1	Not Significant

Pulmonary hypertension is common in SS [2]. Five of the eight patients in our study (62.5%) had pulmonary hypertension and tricuspid regurge. Two patients had pulmonary regurge (37.5%) (table I).

Pericardial effusion was present in two cases (25%) in our study (table I) while Butrous et al. [10] found it in 2 cases (7%) with SS and Anvari et al., in 1992 [11] found it in 3 patients (17%).

Basal echocardiographic findings in patients with SS in our study showed that left ventricular end-diastolic, end-systolic, right ventricular dimensions, left atrial diameter, aortic root diameter and ejection fraction were within normal when compared with the normal range (table II-VI), which agrees with the findings of Butrous et al. [10] who found normal ventricular dimensions, left atrial diameter and aortic diameter in those patients, when he compared them to the normal range as well. However, Gottdiener and coworkers, in 1979 [8] found an increase in left atrial diameter in SS patients and explained this as secondary to rise in left ventricular end-diastolic pressure.

Kazzam and coworkers [12] reported mitral regurge in SS patients and in our study, we found mitral regurge in 2 cases (25%). Mitral valve prolapse was found in one case and thickened mitral valve leaflets and narrowing of the opening in another case (table I).

Improvement of left ventricular contraction parameters after captopril intake was noticed by the statistically significant increase in velocity of circumferencial fiber shortening, posterior wall excursion, velocity of posterior wall excursion and its normalized value, velocity of septal excursion and its normalized value as well as the significant decrease of pre ejection period and its ratio with ejection time (table V-VI). This agrees with Kazzam et al. [13]. They also observed improvement of the diastolic function of left ventricle after captopril intake which was suggested by the increase in mitral E/A. This was also observed in our study (table IV).

Statistical comparison of echocardiographic findings before and after captopril showed no significant change of left ventricular end systolic dimensions, left ventricular volumes in systole and diastole, posterior wall and interventricular septal thickness, left ventricular mass, right ventricular dimensions, right ventricular wall thickness in diastole, septal excursion, ejection fraction or fractional shortening (tables II, III & VI). No significant changes were also observed in left atrial diameter, left ventricular volumes in systole and diastole, posterior wall and interventricular septal thickness, left ventricular mass, right ventricular dimensions, right ventricular wall thickness in diastole, septal excursion, ejection fraction or fractional shortening (tables II, III & VI). No

significant changes were also observed in left artial diameter, aortic diameter, pulmonary artery diameter, left ventricular ejection time, right ventricular ejection time, maximal pulmonary velocity or mean acceleration after captopril intake (tables IV, V & VII).

Acceleration time and its ratio to ejection time increased after captopril intake in both aortic and pulmonary flow which means improvement in the flow of both arteries due to decrease in their resistance (table V & VII).

Vrobel and Cohn in 1980 [5] noticed that patients with resistant congestive cardiac failure on captopril therapy had equivalent reduction in Systemic arterial pressure. Systemic vascular resistance, pulmonary wedge pressure, pulmonary arterial resistance and right atrial pressure. They thus concluded that pulmonary arterial vasodilation occurred in these patients. Treatment with captopril in one patient with primary pulmonary hypertension produced improvement in ventricular function with reduction in systemic and pulmonary vascular resistance, but without fall in pulmonary arterial pressure [14]. The mode of action of angiotensin II converting enzyme inhibitors on the pulmonary circulation remains unknown and may not just be due to a reduction of angiotensin II production, and an increase in kinin levels due to their reduced breakdown is a possible alternative [15]. Kazzam and coworkers in 1991 [13] suggested that the improvement in left ventricular systolic and diastolic function and pulmonary flow with captopril intake is unlikely to be secondary to the effect on the heart rate or blood pressure as they did not change significantly. They suggested that it is likely that captopril exerted its effect by vasodilatation of myocardial vessels causing improvement of myocardial perfusion, decrease of the circulating angiotensin II level or by a direct influence of the local angiotensin system in the heart.

Regarding the pulmonary functions there was a reduction in EVC, FEV1, FEV25-75, PEF and DLO below 80% of predicted values (table VIII). This agrees with Anvari et al. [11]. There was no significant change after captopril intake in any of the spirometric values apart from increased FEV25-75 (table VIII), but it still did not reach the 80% of predicted value (the normal range). Thus, inspite of captopril induced improvement of pulmonary blood flow mediated mostly by decreasing resistance to flow, this did not impart any significant improvement on the respiratory functions. This in part agrees with the findings of Pison and Coworkers in 1991 [16]. They showed that captopril had no effect on the blood gases inspite of the decrease of pulmonary pressure and resistance on patients with chronic bronchitis and pulmonary hypertension.

Conclusion:

Captopril improves left ventricular systolic and diastolic functions and improves pulmonary blood flow in patients whith systemic sclerosis.

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