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Evaluation of the Left Ventricular Function in Patients with Scleroderma with Normal Pulmonary Artery Pressure Using Myocardial Strain Analysis: A Cross-Sectional Study

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ABSTRACT

Background: Since cardiac involvement in scleroderma patients has a poor prognosis, studies have shown that observation of Left Ventricular (LV) deformation analysis using the sensitive speckle-tracking echocardiography (STE) method is appropriate in predicting heart failure.

Objectives: This study evaluated LV function in patients with scleroderma with normal pulmonary artery pressure.

Methods: This cross-sectional study was performed on 30 scleroderma patients and 30 healthy cases by myocardial strain analysis. The frequency of left ventricular dysfunction in systemic sclerosis patients was evaluated by STE, two-dimensional (2D) echocardiography, and Tissue Doppler Imaging (TDI). The statistics analysis was done by SPSS software version 22.

Results: The mean age was 41.07 ± 8.94 years in the case group and 39.00 ± 15.64 years in the control group. The absolute values of the global longitudinal strain (GLS) average, GLS average 3-chambers, ejection fraction, end-diastolic volume (EDV), and stroke volume were significantly lower in the case group compared with the control group ($P < 0.05$). The two groups were similar in other echocardiographic indicators including GLS average 2-chambers, GLS average 4-chambers, heart rate, PAP (mm), and end-systolic volume (ESV) ($P > 0.05$).

Conclusions: Heart health monitoring techniques such as Myocardial Strain Analysis are useful in the early diagnosis of systolic and diastolic disorders and can play an effective role in the early treatment of this disease and prevent permanent cardiac complications of disease or medications in systemic sclerosis patients. Finally, the STE technique can be useful in evaluating GLS to diagnose subclinical LV systolic dysfunction in scleroderma patients.

1. Background

Scleroderma, also known as systemic sclerosis, is a chronic connective tissue autoimmune disease characterized by generalized microangiopathy and progressive fibrosis that affects the skin and several internal organs (1). Increased extracellular matrix deposition occurs, related to immune system abnormalities and endothelial cell damage. Cardiac dysfunction (especially left ventricular) is one of the most important causes of heart failure in patients with scleroderma, resulting in a poor prognosis (2). Since cardiac dysfunction is a significant cause of mortality in these patients, evaluating cardiac function in those without known heart disease is necessary to identify myocardial involvement in its early stages (3).

Since the clinical symptoms of myocardial infarction are highly heterogeneous, its diagnosis is based on a variety of instruments, including specialist examination, electrocardiogram, natriuretic peptide test, magnetic resonance imaging (MRI), and echocardiography. Among these techniques, echocardiography is the most common method for examining systolic and ventricular dysfunction due to its low cost, non-invasiveness, reproducibility,

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and accuracy (4). Diagnosing heart involvement through routine imaging techniques is difficult, and routine echocardiographic techniques and parameters have limited sensitivity for diagnosing left ventricular systolic dysfunction in patients with scleroderma (5, 6). Unfortunately, many cardiac parameters signify the advanced stages of the disease (7), while the predictive indicators of early-stage cardiac involvement are not yet fully established. Therefore, it is crucial to determine the parameters of cardiac function that can be used to diagnose early cardiac involvement in scleroderma patients (8).

Speckle-tracking echocardiography (STE) is a novel non-invasive imaging procedure that permits objective and quantitative assessment of global and regional myocardial work independent of the insonation angle and cardiac movements (9, 10). Studies have shown that observation of left ventricular (LV) deformation analysis using the sensitive STE method in predicting heart failure is appropriate even in cases where ejection fraction (EF) is maintained at normal levels. STE analysis represents a reliable tool for detecting systolic dysfunction (11). In particular, global longitudinal strain (GLS) is a parameter that indicates the percentage of longitudinal shortening (change in length in proportion to baseline length); it is evaluated by STE and analyzed by post-processing of apical images of the LV. A decrease in GLS can be used as a marker of LV dysfunction associated with lower functional capacity and ventricular arrhythmias (12).

2. Objectives

Since scleroderma is associated with pulmonary hypertension and there are conflicting results regarding the association of GLS with scleroderma and pulmonary hypertension, the present study aimed to evaluate LV function in patients with scleroderma with normal pulmonary artery pressure by echocardiography and STE.

3. Patients and Methods

3.1. Design

This cross-sectional study was performed on 30 scleroderma patients over 18 years old with no cardiovascular disease history and 30 healthy controls matched in age and gender. The control group was selected from healthy volunteers with no history of an underlying disease and cardiac or rheumatological problems. The age range in the control group was 20 – 60 years, and participants were selected voluntarily from the personnel of the hospitals and the relatives of the patients.

3.2. Sampling

In this project, we evaluated the frequency of LV dysfunction in scleroderma patients using the GLS. 2D STE was performed at Golestan Hospital, Ahvaz, from January 2021 to December 2021. All patients underwent complete rheumatologic and cardiovascular examinations. A rheumatologist confirmed the diagnosis of scleroderma according to the criteria of the American Rheumatological Association (ACR) and the European Alliance of Associations for Rheumatism (EULAR) (13).

3.3. Eligibility Criteria

Individuals over 18 years of age with no known cardiovascular disease who agreed to participate in the study were included. We excluded those with a history of cardiovascular disease (structural heart disease, heart failure, ischemic heart disease, moderate to severe valvular disease, heart valve replacement, deep vein thrombosis, pulmonary hypertension), pulmonary embolism, malignancy, atrial fibrillation, or a lack of an adequate 2D view for GLS evaluation.

3.4. Data Collection

Data related to the patient's risk factors, including age, gender, family history, medication history, symptoms of disease, systemic problems, and disease duration, were collected from their records using a checklist. The demographic data of all participants were collected. Clinical examinations and echocardiography were done for individuals in both groups. Finally, the obtained information was compared between the scleroderma and control groups.

3.5. Instruments

This study used the Siemens Acuson SC2000 echocardiography device with vendor-independent software (TomTec Image Arena version 4.6).

3.6. Echocardiographic Assessment

Two specialists who had completed expert training in echocardiography made the echocardiographic assessments. All individuals underwent 2D echocardiography, tissue Doppler imaging (TDI), and STE to evaluate LV function. Echocardiographic images of the individuals were taken in the supine position and the left lateral decubitus position at the end of normal breathing, with the minimum depth for the optimal frame rate (40 - 80 fps).

Various echocardiographic indices related to LV systolic and diastolic function, wall movement disorders, and segmental information were measured by 2D STE. The LV ejection fraction (EF) was calculated by Simpson's method and was measured at least three times, and the mean value was calculated for each patient.

In 2D echocardiography, two continuous cardiac cycles were used at relaxation position in 3 standard apical planes (2-chamber, 4-chamber, and long-axis) to measure the systolic peak of the LV GLS of the left ventricle was measured by the software, after confirming the good quality of the tracking by the operator automatically. To check for variations in results between the two operators, 10% of the study population was randomly re-evaluated.

3.7. Data Analysis

The sample size was determined using MedCalc statistical software according to the findings of previous studies, along with 5% error and 90% power, resulting in 30 people for each group. The obtained data were analyzed by descriptive statistics including mean, standard deviation (SD), frequency, and percentage. Data normality was assessed by the Shapiro-Wilk test, and homogeneity of variance was assessed by the Leven test. The t-test of two independent samples (or its non-parametric equivalent,

the Mann-Whitney test) and the chi-squared test were used as appropriate to analyze the data and measure the significance of differences. SPSS software version 22 was used for statistical analysis. A significance level of $P < 0.05$ was considered.

4. Results

The mean age of patients in the scleroderma and control groups was 41.07 ± 8.94 and 39.00 ± 15.64, respectively. In this study, 83.3% (22 people) of the scleroderma patients and 86.7% (26 people) of the controls were females ($P > 0.710$).

Among patients, the mean disease duration in scleroderma patients was 6.33 ± 4.84 years; 100% showed Raynaud's phenomenon, 26.6% digital ulcers, 73.3% puffy hands, 86.7% skin indurations, and 66.7% arthritis. Diastolic dysfunction symptoms were absent in 36.7% and mild in the rest. Regarding the type of scleroderma, 70% had limited scleroderma, and the rest had diffuse scleroderma. Other clinical characteristics of scleroderma patients are presented in Table 1.

Table 2 presents the scleroderma and control groups' demographic characteristics and echocardiography results. There was no significant difference between the groups regarding age, weight, and body mass index ($P > 0.05$). Regarding the echocardiography indices, the absolute GLS average and average 3-chambers (A3C) values were

Table 1. Clinical Characteristics of Scleroderma Patients (n = 30)

Variable		Mean ± SD	Min-Max
Disease duration (years)		6.33 ± 4.84	1 - 17
Medication consumption (years)		5.07 ± 4.81	1 - 17
Variable		Positive (%)	Negative (%)
Telangiectasia		4 (13.3)	26 (86.7)
Interstitial lung disease		4 (13.3)	26 (86.7)
Raynaud's phenomenon		30 (100.0)	0 (0.0)
Digital ulcer		8 (26.6)	22 (73.3)
Puffy hand		22 (73.3)	8 (26.6)
Dysphagia		15 (50.0)	15 (50.0)
Gastroesophageal reflux disease		23 (76.7)	7 (23.3)
Skin induration		26 (86.7)	4 (13.3)
Arthritis		20 (66.7)	10 (33.3)
Variable	Class	N	%
Antibodies	Scl70	22	73.3
	Centromere	8	26.7
Medications	ACEI	2	6.7
	CCB	28	93.3
Diastolic dysfunction	Normal	11	36.7
	Mild	19	63.3
	Moderate	0	0
	Severe	0	0
Scleroderma type	Diffused	9	30.0
	Limited	21	70.0

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; CCB: calcium channel blocker

Table 2. Demographic Characteristics, Left Ventricular Function, and Echocardiographic Parameters in Scleroderma and Control Groups

Variable	Scleroderma Group (Mean ± SD) (n = 30)	Control Group (Mean ± SD) (n = 30)	P-value
Age, years	41.07 ± 8.94	39.00 ± 15.64	0.528
Weight, kg	68.43 ± 9.74	69.00 ± 14.74	0.860
Height, cm	162.23 ± 6.74	157.40 ± 5.88	0.004*
Body mass index, km/m^2	26.08 ± 3.65	27.80 ± 5.48	0.152
GLS average	-19.95 ± 2.87	-21.81 ± 2.35	0.008*
Average 2-chambers	-20.21 ± 3.68	-22.03 ± 2.76	0.071
Average 3-chambers	-18.61 ± 3.19	-22.75 ± 2.87	< 0.001*
Average 4-chambers	-20.14 ± 2.91	-21.18 ± 3.68	0.239
Heart rate	79.43 ± 13.21	79.60 ± 13.72	0.960
Ejection fraction	56.33 ± 6.65	63.13 ± 6.10	< 0.001*
PAP, mmHg	24.03 ± 3.72	23.20 ± 3.81	0.476
End-diastolic volume (EDV)	77.75 ± 18.17	91.87 ± 19.41	0.002*
End-systolic volume (ESV)	33.87 ± 11.20	34.40 ± 10.79	0.581
Stroke volume (SV)	43.79 ± 8.74	57.53 ± 13.77	< 0.001*

*P < 0.05

significantly lower in the scleroderma group compared with the control group ($P < 0.05$). Furthermore, the ejection fraction, end-diastolic volume (EDV), and stroke volume (SV) were significantly lower in scleroderma patients compared with the control group ($P < 0.05$). Other echocardiographic indicators (average 2-chambers, average 4-chambers, heart rate, PAP, and end-systolic volume (ESV) indicated no significant difference between the groups ($P > 0.05$) (Table 2).

5. Discussion

Since scleroderma is linked with pulmonary hypertension, and there is conflicting evidence linking increased GLS with scleroderma and pulmonary hypertension (14-16), we used echocardiography and speckle tracking to assess LV function in patients with scleroderma and normal pulmonary artery pressure. Coghlan et al. conducted a cross-sectional study and presented several pieces of evidence for pulmonary artery hypertension (PAH) in scleroderma. They reported that 87 (19%) out of 466 scleroderma patients had a higher risk of PAH. PAH was reported as mild (64% in WHO functional class I/II) (17). A recent cross-sectional study by Żebryk et al. suggested that individual autoantibodies are associated with specific characteristics like organ failure in scleroderma patients. These researchers considered several cardiac events, such as heart conduction blocks, palpitations, systolic and diastolic dysfunction, loss of ejection fraction, and PAH using Doppler ultrasonography (18).

Spethmann et al. reported the echocardiographic results of comparing LV and GLS functions in the case and control groups. There were no significant changes in HR, PAP, or ESV values ($P > 0.05$) (19). Our findings are in line with Şahin et al., which confirmed subclinical biventricular systolic disorders in patients with scleroderma; however, those results were obtained in the first year of the disease (20). Similarly, Spethmann et al. suggested a slight but significant decrease in longitudinal LV function in patients with scleroderma with preserved LVEF over two years by STE (19).

The slow progression of myocardial fibrosis may cause diffuse subclinical LV dysfunction. Therefore, according to the pattern of changes in longitudinal function, global indicators have been highly emphasized to track systolic function in serial measurements over the years (21-23). Saito et al. examined the prognostic value of the left and right ventricular dysfunction in patients with scleroderma by STE. Impaired GLS and global circumferential strain (GCS) values were associated with severe dysfunction. However, patients with high pulmonary artery pressure were also evaluated in their study, representing a point of difference from our study (24). Dedeoglu et al. examined cardiac involvement in adolescent scleroderma by 3D echo and reported significant differences in LV systolic and diastolic diameters. They also stated that the values of GLS and GCS in the patient group were significantly impaired compared to the control group, which is consistent with the results of our study (25). Tadic et al. and Tona et al. studied the cardiac function of scleroderma patients by echocardiography, reporting that LV function is affected by scleroderma (26, 27).

This study was limited by its single-center nature and the potential bias caused by operator dependence regarding echocardiographic measurements. To eliminate such bias, both specialists performing echocardiography had undergone expert training programs, and 10% of the study population was randomly re-evaluated, revealing similar results to the first evaluation. Hence, our study findings indicate the value to

5.1. Conclusions

The STE technique can be useful in evaluating GLS and diagnosing subclinical LV systolic dysfunction in scleroderma patients. The absolute GLS and A3C values were significantly lower in patients with scleroderma than in healthy controls. LV volume measurement is a key finding in accurate LVEF measurement. We suggest conducting a similar study on different populations with larger sample sizes and using other methods, such as cardiovascular magnetic resonance (CMR) imaging, to evaluate myocardial function in patients with scleroderma. Additionally, comparing the accuracy of CMR and GLS in assessing the myocardial function of scleroderma patients can provide useful data. We also suggest regular monitoring of cardiac function by STE to evaluate GLS in scleroderma patients.

5.2. Ethical Approval

This study was approved under the ethical approval code IR.AJUMS.HGOLESTAN.REC.1399.062.

5.3. Informed Consent

We obtained written informed consent from each participant to participate in this study.

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Authors' Contribution

ER designed and supervised the study, NPI collected the data, NA analyzed the results, MM checked the cardiac involvement by speckle-tracking echocardiography, KM revised the manuscript.

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The authors have no financial interests related to the material in the manuscript.

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