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Original Article / *Klinik Çalışma - Araştırma*

Assessment of Subclinical Cardiac Dysfunction in Diffuse Scleroderma Patients

Diffüz Skleroderma Hastalarında Subklinik Kardiyak Fonksiyonların Değerlendirilmesi

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Objectives: We aimed to evaluate left and right ventricular functions with different echocardiographic methods in asymptomatic patients with diffuse scleroderma (SSc).

Patients and Methods: Twenty diffuse SSc outpatients, asymptomatic with regard to cardiac symptoms and twenty healthy control subjects were enrolled. Conventional left ventricular (LV) and right ventricular (RV) echocardiographic measurements, pulsed wave tissue Doppler imaging (TDI) and myocardial performance indexes (MPI) were evaluated.

Results: Both left (LV early to atrial peak velocity ratio: p<0.02, LV isovolumic relaxation time: p<0.03, LV deceleration time: p<0.02) and right ventricle (RV early to atrial peak velocity ratio: p<0.02) diastolic functions were significantly reduced in SSc group while the parameters assessing LV systolic function were similar in both groups. Pulmonary artery pressure was significantly higher in 25% of SSc patients (31.1±5.2 and 24.7±2.7 mmHg, p<0.001). Although mitral and tricuspid annular systolic velocities with TDI (Sm, St) were similar between two groups, obtained diastolic functions showed a decrease in SSc patients. Tei index was statistically higher in SSc group (left ventricle MPI (LV-MPI): p<0.03 and right ventricle MPI (RV-MPI): p<0.007).

Conclusion: Diastolic dysfunction of both ventricles with different echocardiographic methods was observed in diffuse SSc patients even without cardiac symptoms.

Key words: Systemic sclerosis; cardiac dysfunction; echocardiography; tissue Doppler imaging (TDI); myocardial performance indexes (MPI).

Amaç: Asemptomatik diffüz skleroderma (SSc) hastalarında sağ ve sol ventrikül fonksiyonlarının değişik ekokardiyografik yöntemler ile değerlendirilmesi amaçlanmıştır.

Hastalar ve Yöntemler: Çalışmaya kardiyak açıdan asemptomatik olan 20 diffüz SSc tanılı ayaktan hasta ile 20 sağlıklı kontrol dahil edildi. Konvansiyonel ekokardiyografik yöntemler ile sol (LV) ve sağ (RV) ventrikül ölçümleri, doku Doppler görüntüleme (TDI) ve miyokard performans indeksleri (MPI) değerlendirildi.

Bulgular: Skleroderma tanılı hastalarda hem sol hem de sağ ventrikül diyastolik fonksiyonları belirgin olarak azalmış olmakla birlikte, LV sistolik fonksiyonları her iki grupta benzer bulundu. SSc hastalarının %25'inde pulmoner arter basıncının artmış olduğu gözlendi (31.1±5.2 ve 24.7±2.7 mmHg, p<0.001). TDI ile mitral ve triküspid anüler sistolik hızlarının her iki grupta benzer olduğu saptanırken, SSc hastalarında diyastolik fonksiyonların azaldığı görüldü. Tei indeksinin SSc grubunda her iki ventrikül için de istatistiki olarak artmış olduğu saptandı (LV-MPI: p<0.03 ve RV-MPI: p<0.007).

Sonuç: Kardiyak açıdan asemptomatik diffüz SSc hastalarında, farklı ekokardiyografik yöntemler ile, her iki ventrikül diyastolik disfonksiyonun bulunduğu gözlenmiştir.

Anahtar sözcükler: Skleroderma; kardiyak disfonksiyon; ekokardiyografi; doku Doppler görüntüleme (TDI); miyokard performans indeksi (MPI).

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Systemic Sclerosis (SSc) is a multisystem disease that effects the skin, gastrointestinal tract, lung, heart, kidney and peripheral nervous system. The extent and severity of internal organ involvement are the most important factors influencing the disease outcome and prognosis in SSc. Until recent years it has been considered that cardiac and pulmonary involvement were the main determinants of the overall prognosis of the disease.[1,2] However, with the help of different diagnostic methods and clinical observations, it has been proven that heart is more frequently and severely involved in SSc. Recent studies have suggested that clinical evidence of myocardial disease may be found in 20% to 25% of patients with SSc.[3]

Systemic Sclerosis heart involvement (SHI) may present itself with a variable pattern of clinical manifestations. Most frequent symptoms are palpitations which may result from various ventricular and supraventricular arrhythmias, angina pectoris caused by pericarditis and coronary vasoconstriction, dyspnea related to congestive heart failure and malign arrhythmias resulting with death.[1,2,4-7] It is easy to trace cardiac involvement in symptomatic patients, but what about patients with no cardiac symptoms? Is it possible that there might be a subclinical cardiac involvement with deteriorating systolic or diastolic function? In this study we aimed to evaluate silent cardiac involvement with different echocardiographic methods in asymptomatic patients with diffuse SSc.

PATIENTS AND METHODS

Study Population

We consecutively selected twenty asymptomatic diffuse SSc outpatients (18 women; age range 24-63; mean 44±9.6 years) who referred to the division of Rheumatology at İstanbul University and a sex and age matched group of twenty healthy control subjects (18 women; age range 25-64; mean 41±10 years). All patients had Raynaud's phenomenon and none had positive anti-centromere antibodies but had 60% were positive for anti-Scl 70. Cardiac symptoms including dyspnea were absent in all patients. Routine chest x-rays and pulmonary function tests were incompatible with lung involvement. Six minute walk distance and arterial pulse oxygen saturation levels were also in normal ranges. None of the patients included to the study had evidence of hypertension, renal involvement, diabetes or any other systemic disease. Written informed consent was obtained from all patients and study protocol was approved by our institutional review board. All patients met American College of Rheumatology 1980 preliminary criteria for the classification of SSc.[8] Fifteen scleroderma patients (75%) were using calcium antagonists (CA), while three patients (%15) were using angiotensin-converting inhibitors (ACEI) for Raynaud phenomenon.

All patients and control subjects were questioned about cardiac history and examined with electrocardiography to consider cardiac involvement. Patients with any cardiac symptoms were excluded. Patients with hypertension, atrial fibrillation, complete heart block, changes referring to myocardial infarction on ECG and the other connective tissue diseases, major organ involvement and malignancy were excluded.

Echocardiographic Examination

Echocardiographic examination was performed using a Vingmed System Five, Norway echocardiographic system equipped with 2.5-MHz transducers (Vingmed Sound, Norway). M-Mode and two-dimensional measurements were performed in accordance with methods recommended by the American Society of Echocardiography.[9,10]

Conventional left ventricular (LV) and right ventricular (RV) echocardiographic measurements were performed in all subjects. Measurements included LV deceleration time (LV-DT), LV isovolumic relaxation time (LV-IVRT), LV early to atrial peak velocity ratio (LV-E/A), RV early to atrial peak velocity ratio (RV-E/A). Left ventricular ejection fraction (LV-EF) was measured by using the Teichholtz formula.[11]

Pulsed wave tissue Doppler imaging (TDI) was performed by activating the TDI function of the same machine. The spectral pulsed Doppler signal was arranged to obtain a Nyquist limit of 15-20 cm/s with the lowest wall filter settings. From the apical four-chamber view, a 5 mm sample volume was located at the ventricle free wall near to the lateral tricuspid and the posterior mitral leaflets. The resulting velocities were recorded for five cycles at a sweep speed of 50 mm/s and stored on a videotype for later analysis. Following parameters were determined: peak systolic mitral annular velocity (Sm), peak early diastolic mitral annular velocity (Em), peak late diastolic mitral annular velocity (Am), mitral Em/Am ratio, peak systolic tricuspid annular velocity (St), peak early diastolic tricuspid annular velocity (Et), peak late diastolic tricuspid annular velocity (At) and tricuspid Et/At ratio.[10]

Left and right ventricular functions were also investigated by using myocardial performance index (MPI). Myocardial performance index was calculated by the formula: MPI = (Isovolumic contraction time + isovolumic relaxation time) / (ejection time).[11]

The Doppler imaging calculations of both left and right ventricles were performed during the end of the expirium.

Pulmonary artery pressures (PAP) were calculated by the modified Bernoulli equation in patients with tricuspid regurgitation.[12] In this study PAP were figured both in two groups only who had tricuspid regurgita-

Table 1: Demographic features, hemodynamic and biochemistric parameters

	Scleroderma n=20	Control n=20	*p*
Age (years)	44±9.6	41±10	NS
Male	2/20	2/20	NS
BMI (kg/m2)	22±3.2	23±5.6	NS
Systolic (mmHg)	126±23	121±16	NS
Diastolic (mmHg)	76±11	79±9	NS
Heart rate (beats/min)	74±6	66±5	0.001
Glucose (mg/dl)	88±12	90±14	NS
Creatinine (mg/dl)	0.9±0.2	0.8±0.1	NS
Hb (g/dl)	11.3±2.1	12.3±3.2	NS
ACEI/CA	3/15	-	-
Steroid/Methotrexate	4/5	-	-

BMI: Body mass index; Hb: Hemoglobin; ACEI: Angiotensin-converting enzyme inhibitors; CA: Calcium antagonists; NS: Not significant.

tion; 16 in the scleroderma group and 15 in the control group.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0 for Windows. Comparison of groups was performed using Mann-Whitney U and chi-square tests. Mann-Whitney U test was applied to the groups in pairs, for all possible combinations. p less than 0.05 is considered statistically significant. All values are expressed as mean ± SD.

RESULTS

Baseline clinical, biochemistrical and demographic characteristics are listed in Table 1. Only the heart rate was significantly higher in the diffuse SSc group while the other parameters were similar (Table 1).

When we compared the echocardiographic findings evaluated from conventional methods, we established that both left (LV-E/A ratio: p<0.02, LV-IVRT: p<0.03, LV-DT: p<0.02) and right ventricle (RV-E/A ratio: p<0.02) diastolic functions were significantly reduced in SSc group while the parameters assessing LV systolic function were similar in SSc and control groups (Table 2). Furthermore the PAP measurements were assigned significantly higher in 25% of the patients in the SSc group (31.1±5.2 and 24.7±2.7 mmHg, p<0.001).

Table 2: Echocardiographic measurements of left ventricle

	Scleroderma n=20	Control n=20	*p*
LV-EF (%)	63±5	66±5	NS
LV-E/A	1.1±0.4	1.4±0.2	0.02
LV-IVRT (msn)	117±14	106±11	0.03
LV-DT (msn)	196±35	170±18	0.02
Sm (m/sn)	9.1±2.5	10±2.4	NS
Em/Am	1.1±0.1	1.6±0.2	0.01
LV-MPI	0.55±0.1	0.41±0.05	0.03
PAP (mmHg)	31.1±5.2	24.7±2.7	<0.001

LV: Left ventricle; EF: Ejection fraction; E/A: Early to atrial peak velocity ratio; IVRT: Isovolumic relaxation time; DT: Deceleration time; Sm: Peak systolic mitral annular velocity; Em: Peak early diastolic mitral annular velocity; Am: Peak late diastolic mitral annular velocity; MPI: Myocardial performance index; PAP: Pulmonary artery pressure; NS: Not significant.

Although mitral and tricuspid annular systolic velocities with TDI (Sm, St) were similar between two groups, the obtained diastolic functions showed a decrease in SSc patients than the control group, parallel to the results from prior conventional measurements (left ventricle Em/Am: p<0.01, right ventricle Et/At: p<0.03) (Table 2 and 3).

We evaluated that for MPI measurements, Tei index was statistically higher in SSc group (left ventricle MPI (LV-MPI): p<0.03 and right ventricle MPI (RV-MPI): p<0.007) (Table 2 and 3).

DISCUSSION

The left and right ventricular myocardial performance index representing global ventricular functions was higher in SSc group. In other words, left and right ventricular global functions were depressed in patients with scleroderma. Besides global dysfunction, diastolic dysfunction of both ventricles were also detected by conventional and new methods such as TDI. Tei index assesses the global functions of the ventricles and is not influenced by factors such as pre-load and after-load. This index has also been reported to be independent of heart rate.[13-15] Diastolic dysfunction was also detected by TDI which is not affected by heart rate.[13,14] Since both ventricular systolic functions were normal, it seems MPI to be influenced mainly by diastolic dysfunction of the left and right ventricles. So, we suggest that the subclinical myocardial involvement is evident in scleroderma patients even with no cardiac symptoms and this may be important because heart involvement is one of the most important prognostic factors.[1,2]

By the help of conventional echocardiographic methods, several studies indicate diastolic dysfunction, but systolic dysfunction is not so frequently evaluated. Some of the recent studies done with using tissue Doppler imaging showed disturbed right ventricular diastolic

Table 3: Echocardiographic measurements of right ventricle

	Scleroderma n=20	Control n=20	*p*
RV-E/A	1.1±0.1	1.4±0.3	0.02
St (m/sn)	13.3±2.6	13.7±1.6	NS
TDI-E/A	0.9±0.2	1.2±0.4	0.03
RV-MPI:	0.43±0.1	0.30±0.05	0.007

RV: Right ventricle; E/A: Early to atrial peak velocity ratio; St: Peak systolic tricuspid annular velocity; TDI: Tissue Doppler imaging; MPI: Myocardial performance index; NS: Not significant

function in patients with systemic sclerosis.[16] We also found consistent results about both right and left ventricle functions and were similar to these mentioned studies. Even most of the studies investigated left ventricle functions[17,18], this is one of the few studies that evaluates right ventricle functions with different echocardiographic methods.

Decrease in wall elasticity and incomplete relaxation resulting from myocardial fibrosis are the major factors creating diastolic dysfunction.[4,5] The underlying mechanism of the detected myocardial dysfunction may be either the focal myocardial lesions ranging from constructive band necrosis to fibrosis[4-6] or the reversible vasospastic abnormalities in small coronary arteries[19,20] or both. Since there has been studies indicating myocardial perfusion defects in these patients,[7,21] ischemia seems to be a reasonable cause of myocardial dysfunction.

In our study we observed increased PAP levels in 25% of SSc patients. Pulmonary arterial hypertension (PAH) is an important cause of mortality and morbidity that occurs in up to 27% of patients with SSc.[22] In limited cutaneous SSc, PAH is the major cause of mortality and is usually isolated (i.e., without interstitial lung disease).[23] Whereas, approximately half of the cases of PAH in diffuse SSc are associated with pulmonary fibrosis and half are not.[24] A recent study in diffuse SSc defined 21% isolated PAH in their cohort which is also similar to our study.[25] Some recent reviews about heart involvement in SSc suggest that, regardless of interstitial lung disease, myocardial involvement by patchy fibrosis may lead to ventricular diastolic dysfunction, whereas right ventricle overload and failure may complicate pulmonary hypertension.[26] The frequency and effect of isolated PAH has never been investigated and requires additional study.

Unfortunately, in this study we couldn't perform right heart catheterization to confirm PAH that it wasn't the main objective of our study. Since the presenting symptoms of mild to moderate PAH are not disease specific, it is often underrecognized. Because of that, it is recommended to screen all asymptomatic SSc patients annually.[27]

Our data show that, there is possibly diastolic dysfunction of both ventricles in diffuse SSc patients with no cardiac symptoms.

REFERENCES

1. Arias-Nuñez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, et al. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. Medicine 2008;87:272-80.
2. Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis 1998;57:682-6.
3. Meune C, Avouac J, Wahbi K, Cabanes L, Wipff J, Mouthon L, et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: A controlled study of 100 consecutive patients. Arthritis Rheum 2008;58:1803-9.
4. D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. Am J Med 1969;46:428-40.
5. Bulkley BH, Ridolfi RL, Salyer WR, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976;53:483-90.
6. Deswal A, Follansbee WP. Cardiac involvement in scleroderma. Rheum Dis Clin North Am 1996;22:841-60.
7. Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis. Rheumatology 2006;45 Suppl 4:iv14-7.
8. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.
9. Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, et al. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. Circulation 1980;62:212-7.
10. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072-83.
11. Di Bello V, Lattanzi F, Picano E, Talarico L, Caputo MT, Di Muro C, et al. Left ventricular performance and ultrasonic myocardial quantitative reflectivity in endurance senior athletes: an echocardiographic study. Eur Heart J 1993;14:358-63.
12. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657-62.
13. Alam M, Wardell J, Andersson E, Samad BA, Nordlander R. Characteristics of mitral and tricuspid annular velocities determined by pulsed wave Doppler tissue imaging in healthy subjects. J Am Soc Echocardiogr 1999;12:618-28.
14. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 1995;26:135-6.
15. Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, et al. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr 1996;9:838-47.
16. Lindqvist P, Caidahl K, Neuman-Andersen G, Ozolins C, Rantapää-Dahlqvist S, Waldenström A, et al. Disturbed right ventricular diastolic function in patients with systemic sclerosis: a Doppler tissue imaging study. Chest 2005;128:755-63.
17. Maione S, Cuomo G, Giunta A, Tanturri de Horatio L, La Montagna G, Manguso F, et al. Echocardiographic alterations in systemic sclerosis: a longitudinal study. Semin Arthritis Rheum 2005;34:721-7.
18. D'Andrea A, Caso P, Cuomo S, Scotto di Uccio F, Scarafile R, Salerno G, et al. Myocardial and vascular dysfunction in systemic sclerosis: the potential role of noninvasive assessment in asymptomatic patients. Int J Cardiol 2007;121:298-301.
19. Alexander EL, Firestein GS, Weiss JL, Heuser RR, Leitl G, Wagner HN Jr, et al. Reversible cold-induced abnormalities in myocardial perfusion and function in systemic sclerosis. Ann Intern Med 1986;105:661-8.

20. Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. Lancet 1989;2:475-9.
21. Belloli L, Carlo-Stella N, Ciocia G, Chiti A, Massarotti M, Marasini B. Myocardial involvement in systemic sclerosis. Rheumatology 2008;47:1070-2.
22. Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Intern Med J 2007;37:485-94.
23. Morelli S, Barbieri C, Sgreccia A, Ferrante L, Pittoni V, Conti F, et al. Relationship between cutaneous and pulmonary involvement in systemic sclerosis. J Rheumatol 1997;24:81-5.
24. Chang B, Wigley FM, White B, Wise RA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. J Rheumatol 2003;30:2398-405.
25. Trad S, Amoura Z, Beigelman C, Haroche J, Costedoat N, Boutin le TH, et al. Pulmonary arterial hypertension is a major mortality factor in diffuse systemic sclerosis, independent of interstitial lung disease. Arthritis Rheum 2006;54:184-91.
26. Ferri C, Giuggioli D, Sebastiani M, Colaci M, Emdin M. Heart involvement and systemic sclerosis. Lupus 2005;14:702-7.
27. British Cardiac Society Guidelines and Medical Practice Committee, and approved by the British Thoracic Society and the British Society of Rheumatology. Recommendations on the management of pulmonary hypertension in clinical practice. Heart 2001;86 Suppl 1:I1-13.