Evaluation of aortic elastic properties in patients with systemic sclerosis

Sistemik sklerozlu hastalarda aortanın esneyebilirlik özelliklerinin değerlendirilmesi

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ABSTRACT

Objectives: The aim of this study was to investigate the elastic properties of the aorta, which are known to be predictors of cardiovascular morbidity and mortality in patients with systemic sclerosis (SSc).

Study design: Forty patients (2 males, 38 females) with SSc who had been referred to echocardiography without any exclusion criteria were enrolled in the study. The control group consisted of 38 subjects (4 males, 34 females) who were examined in the cardiology out-patient clinic and referred to echocardiography for any indication in the same period. Parameters related to diastolic functions of the left ventricle were obtained by echocardiography and the following parameters of aortic elasticity were calculated according to these formulas: aortic strain = ([AOS - AOD]/AOD), aortic stiffness index (□) = ln (systolic blood pressure/diastolic blood pressure)/aortic strain and aortic distensibility = 2 × aortic strain/pulse pressure.

Results: Aortic strain and distensibility were significantly lower, and aortic stiffness index □ was significantly higher in the SSc group compared to the control group. While the systolic diameter of the aorta did not differ between study and control groups, the diastolic diameter of the aorta was significantly higher in SSc patients. On the other hand, left ventricular diastolic functions were compromised in the SSc group. Mitral A velocity, E-wave deceleration time and E/Em ratio were increased and mitral E/A ratio, lateral and medial annular Em velocity were significantly decreased in SSc patients.

Conclusion: Our study demonstrated that aortic stiffness is increased and left ventricular diastolic functions are compromised in patients with SSc.

ÖZET

Amaç: Bu çalışmada, sistemik sklerozlu hastalarda kardiyovasküler mortalite ve morbiditenin belirteçleri olarak değerlendirilen aortun elastik özelliklerinin incelenmesi amaçlanmıştır.

Çalışma planı: Dışlanma kriterleri olmayan ve ekokardiyografi uygulanan 40 hasta (2 erkek, 38 kadın) çalışmaya alındı. Kontrol grubu aynı dönem içinde kardiyoloji polikliniğinde görülen ve herhangi bir nedenle ekokardiyografi uygulanan 38 kişiden (4 erkek, 34 kadın) oluşmaktadır. Ekokardiyografik olarak sol ventrikül diyastolik fonksiyonu ile ilgili parametreler elde edilerek, aortun elastik özellikleri aşağıdaki formüller kullanılarak hesaplandı. Aort gerilimi = [(AOS - AOD)/AOD], aort sertliği indeksi (β) = ln (sistolik kan basıncı/diyastolik kan basıncı)/aortik strain ve aort esnekliği = 2 x aortik strain/nabız basıncı.

Bulgular: Aort gerilimi ve esneklik kontrol grubu ile kıyaslandığında sistemik sklerozlu hastalarda anlamlı olarak düşük iken, aort sertliği indeksinin daha yüksek olduğu saptandı. Aortanın sistolik çapında iki grup arasında anlamlı bir fark gözlenmezken hasta grubunda diyastolik çapın belirgin olarak büyük olduğu gözlendi. Diğer taraftan sistemik sklerozlu hastalarda sol ventrikül diyastolik fonksiyonlarının bozulduğu tespit edildi. Çalışma grubunda mitral A velositesi, E dalgası deselerasyon zamanı ve E/Em oranının arttığı, öte yandan mitral E/A oranının, lateral ve mediyal anüler Em velositelerinin ise anlamlı oranda azaldığı gözlendi.

Sonuç: Sonuç olarak bu çalışma sistemik sklerozlu hastalarda aorta katılığının arttığını ve sol ventrikül diyastolik fonksiyonlarının bozulduğunu göstermektedir.

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Atherosclerosis is regarded as a combination of two major separate diseases: atherosis and sclerosis. The sclerosis component depends on deterioration of aortic elastic properties and is called aortic stiffness. The stiffness of the aorta influences aortic conduit function, causing pressure elevation and an abnormal pressure pattern that increases the afterload of the left ventricle. Consequently, increased aortic stiffness may induce left ventricular hypertrophy and may alter left ventricular diastolic and systolic functions.[1] It is well known that aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in a different group of patients.[2]

Abbreviations:

AI	*Augmentation index*
AOD	*Diastolic aortic diameter*
AOS	*Dystolic aortic diameter*
CI	*Confidence interval*
DTI	*Doppler tissue imaging*
FMD	*Flow-mediated dilatation*
PW	*Posterior wall*
PWV	*Pulse wave velocity*
SSc	*Systemic sclerosis*

Systemic sclerosis (SSc) is a chronic autoimmune disease that affects the skin and various internal organs. The most characteristic histopathological alteration of SSc is an extensive accumulation of extracellular matrix.[3] The resulting fibrosis disrupts the physiological tissue structure and frequently leads to dysfunction of the affected organs.[4] In addition to fibrosis, vascular changes are a major hallmark of SSc. These may be classified as destructive and proliferative vasculopathy. Destructive vasculopathy affects small vessels and manifests early in the course of SSc as a progressive loss of capillaries and insufficient angiogenesis. In contrast, proliferative vasculopathy is characterized by proliferation of vascular cells with obstruction of the lumen, affects larger vessels like the pulmonary arteries and often manifests later in the course of the disease as pulmonary arterial hypertension.[3] In addition, alterations in the physical properties of peripheral arteries, such as increased rigidity and impaired distensibility, i.e. increased arterial stiffness, have been reported.[5-9] As mentioned above, SSc may lead to arterial dysfunction and premature aging of the arteries. This coexistence of SSc and vasculopathy brings to mind the hypothesis that SSc and vascular damage may be ethiopathogenetically related. The pathogenetic mechanisms underlying macrovascular pathology in SSc are thought to depend on the degree of the ongoing inflammatory fibrotic process, the hallmark of the disease.[7,10] Whether vascular compromise extends to large arteries such as the aorta, and the mechanism of this process have not been fully understood.

The aim of this study is to investigate the elastic properties of the aorta, which are known to be predictors of cardiovascular morbidity and mortality in patients with SSc.

PATIENTS AND METHODS

Study protocol

This study was designed with the collaboration of the cardiology and rheumatology clinics in our hospital. The study population with SSc was enrolled from patients who were being followed up in the rheumatology outpatient clinic, while the control group consisted of patients from the cardiology out-patient clinic. After acquiring the patients' informed consent, echocardiographic examinations were practiced. The study conforms with the ethical principles of the Helsinki Declaration.

Between December 1st 2007 and December 31st 2009, 40 patients (2 male, 38 female) with SSc, who had been referred to echocardiography without any exclusion criteria, were enrolled in the study. The control group consisted of 38 subjects (4 male, 34 female), who were examined in the cardiology out-patient clinic and referred to echocardiography for any indication in the same period.

Exclusion criteria were lack of informed consent and existence of hypertension, diabetes, chronic obstructive pulmonary disease, coronary artery disease, chronic renal disease, atrial fibrillation, left bundle branch block, right bundle branch block, pacemaker or implantable cardioverter defibrillator, collagen vascular diseases other than scleroderma, rheumatic heart valve disease, and heart valve prosthesis.

General examination and measurements

Clinical histories of all patients were recorded, and a general physical examination was carried out. Age, sex, weight, height, body surface area, body mass index, blood pressure and heart rate measurements of the patients and control group were acquired. Blood pressure measurements were made with a mercuric sphygmomanometer under the guidance of ESH/ESC 2007 Arterial Hypertension Guideline simultaneously with the echocardiographic examination. SSc severity was assessed according to the Medsger scale, which includes a general status of the patient, peripheral vascular, skin, joint, tendon, muscle, gastrointestinal tract, lung, and kidney involvement.[11]

Echocardiographic assessment

Echocardiographic examination was performed with a commercially available device (General Electric, Vivid 7 Pro, Vingmed Ultrasound AS, Horton, Norway) using a 2.5-3.5 MHz transducer in the lateral decubitis position according to the American Society of Echocardiography guidelines, with a simultaneously recorded electrocardiogram. Left atrium diameter and aortic diameter were measured on M-mode tracing at aortic sinus valsalva level in the parasternal long axis view, and left ventricle end-systolic diameter, left ventricle end-diastolic diameter, posterior wall (PW) and interventricular septum thickness were measured on the M-mode tracing at the papillary muscle level.

Parameters related to diastolic functions of the left ventricle were obtained as follows: sample volume (size 2 mm) of the pulsed wave Doppler was placed between the tips of the mitral leaflets in the apical four-chamber view. Early (E) and late (A) transmitral flow velocities, the ratio of early to late peak velocities (E/A) and deceleration time of E velocity were obtained. Pulsed wave Doppler tissue imaging (DTI) was performed by activating the DTI function of the machine. Sample volume was located at the lateral and septal side of the mitral annulus. Early (Em) and late (Am) diastolic and systolic (Sm) mitral annulus velocities were measured. Doppler echocardiograms were recorded on a strip chart recorder with a sweep speed of 100 mm/s; the values of three different cardiac cycles were averaged. The diameter of the ascending aorta was measured in the parasternal long axis view by M-mode tracing at a level of 3 cm above the aortic valve. Systolic aortic diameter (AOS) was measured at the maximal anterior motion of the aorta, while diastolic aortic diameter (AOD) was measured at the peak of the QRS complex on the simultaneously recorded electrocardiogram. Five consecutive measurements were averaged. Aortic elasticity parameters were calculated according to the following formulas:

- Aortic strain = ([AOS − AOD]/AOD)
- Aortic stiffness (β) index = ln (systolic blood pressure/diastolic blood pressure)/aortic strain
- Aortic distensibility = 2 × aortic strain/pulse pressure

Statistical analyses

Analyses were performed, using the MedCalc® (Version 11.3.8.0) pocket program. Numerical data were expressed as the mean±standard deviation and were tested for a normal distribution using the Kolmogorov-Smirnov test. Comparisons between groups were made using Student's independent t-test for normally distributed data (strain) or the Mann-Whitney U-test for non-normal distributed data (stiffness, distensibility). Difference between categorical variables was assessed using the chi-square or Fisher's exact test. The correlation coefficient was calculated using Pearson analysis. The results were considered as significant when $p<0.05$.

RESULTS

Forty patients with SSc (mean age 49.8±9.4 years; 38 female, 2 male) and 38 controls (mean age 46.2±13.7 years; 34 female, 4 male) were enrolled in the study. The patient and control groups were age- and gender-matched. Clinical characteristics of the patient group are given in Table 1. Eleven patients (27.5%) had diffuse and 29 patients (72.5%) had localized SSc.

Table 1. Clinical and laboratory parameters of the SSc group (n=40)

	Mean±SD
Fasting blood glucose (mg/dl)	89.7±23.6
Blood urea (mg/dl)	33.2±25.3
Creatinine (mg/dl)	0.91±1.06
Haemoglobin (g/dl)	12.5±1.62
Haematocrit (%)	36.9±4.32
White blood cell count (mm³)	7441.2±2756.7
Median neutrophil count (mm³)	3655 (1700-13160)
Median lymphocyte count (mm³)	1675 (500-4500)
Median neutrophil/lymphocyte ratio	2.4 (0.78-11.5)
Platelet count (mm³)	263852.9±82936.7
Total cholesterol (mg/dl)	194.2±46.3
LDL-C (mg/dl)	115.5±33.3
HDL-C (mg/dl)	51.2±19.4
Triglycerides (mg/dl)	133.9±59.9
Median hs-CRP (mg/L)	6.43 (3.02-99.1)
ESR (mm/h)	31.8±19.8
Medsger disease severity score	5.18±2.5

LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; hs-CRP: High sensitivity C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 2. Comparison of echocardiographic measurements between the study and control groups

	SSc (n=40)	Control (n=38)	*p*
Left atrium (cm)	3.4±0.48	3.3±0.46	0.2845
Interventricular septal thickness (cm)	0.89±0.17	0.90±0.13	0.8376
Posterior wall thickness (cm)	0.85±0.16	0.82±0.13	0.3466
End-diastolic diameter (cm)	4.45±0.43	4.51±0.33	0.4368
End-systolic diameter (cm)	3.39±4.24	2.77±0.21	0.3750
Fractional shortening (%)	38.5±6.7	38.5±5.1	0.9746
Ejection fraction (%)	67.1±7.4	68.4±5.1	0.338

SSc: Systemic sclerosis.

The mean Medsger scale of the patient group was 5.18±2.5. The prominent involvement was vascular (Raynaud) and skin-joint in half of the patients. 14 (35%) had varying degrees of pulmonary fibrosis. 6 (15%) patients had significant gastrointestinal tract involvement. Fourteen were on a calcium channel blocker, 22 on steroid therapy. Fifteen used immunosuppressive agents (azathiopurine, cyclophosphamide or methotrexate). Nearly all patients were on renin-angiotensin-aldosterone blocking agents and aspirin therapy. The comparison of study and control groups by means of echocardiographic measurements is given in Table 2. Left atrial diameter, left ventricular end-systolic and end-diastolic diameter, thickness of the interventricular septum and PW, left ventricular ejection fraction, and fractional shortening were not statistically different between the two groups (Table 2). Factors that may affect elastic properties of aorta such as age, gender, body surface area, body mass index, systolic and diastolic blood pressure, pulse pressure and heart rate were similar between the two groups (Table 3). The comparison of elastic properties of the aorta between two groups is given in Table 3. Aortic strain and distensibility were significantly lower, and aortic stiffness index β was significantly higher in the SSc group compared to the control group. While the systolic diameter of the aorta did not differ between study and control groups, the diastolic diameter of the aorta was significantly higher in SSc patients (Table 3). Left ventricular diastolic functions were compro-

Table 3. Elastic properties of the aorta and related factors in study and control groups

	SSc (n=40)	Control (n=38)	*p*
Age (years)	49.8±9.4	46.2±13.7	0.1781
Gender (%)			
Female	38 (95)	34 (89.5)	0.4254
Male	2 (5)	4 (10.5)	
Body surface area (m²)	1.64±0.14	1.69±0.13	0.1068
Body mass index (kg/m²)	26.8±5.2	28.1±5.0	0.2778
Systolic blood pressure (mmHg)	118.1±24.9	123.9±20.8	0.2804
Diastolic blood pressure (mmHg)	75±13.6	80.9±13.6	0.0713
Pulse pressure (mmHg)	42.9±16.7	42.8±15.4	0.9709
Systolic diameter of the aorta (cm)	3.00±0.44	2.84±0.38	0.0901
Diastolic diameter of the aorta (cm)	2.8±0.45	2.5±0.35	0.0029
Strain	7.41±3.62	13.4±6.4	**<0.0001**
Stiffness index β	7.16 (2.69-46.16)	3.72 (1.59-16.71)	**<0.0001**
Distensibility	0.002968 (0.000595-0.04138)	0.005590 (0.001235-0.01361)	**<0.0001**

SSc: Systemic sclerosis.

Table 4. Comparison of left ventricular diastolic parameters between SSc and control groups

	SSc (n=40)	Control (n=38)	*p*
Mitral E velocity (m/s)	0.79±0.22	0.80±0.14	0.8369
Mitral A velocity (m/s)	0.83±0.34	0.66±0.17	0.0105
Mitral E/A ratio	1.07±0.47	1.26±0.31	0.0433
Deceleration time (ms)	179.7±32.6	161.5±28.4	0.0114
Lateral Em (m/s)	0.12±0.038	0.15±0.038	0.0005
Lateral E/Em ratio	7.4±3.0	5.7±1.4	0.0027
Lateral Am (m/s)	0.12±0.027	0.11±0.036	0.0712
Lateral Sm (m/s)	0.10±0.022	0.11±0.021	0.1660
Medial Em	0.09±0.029	0.11±0.031	0.0002

SSc: Systemic sclerosis.

Table 5. Correlation coefficients between inflammation markers and aortic stiffness indices

	Aortic strain	Stiffness index (β)	Aortic distensibility
High sensitivity C-reactive protein	r=0.00255	r=–0.00692	r=0.00406
	p=0.8650	p=0.6595	p=0.7962
White blood cell count	r=–0.2582	r=0.2750	r=0.05109
	p=0.0733	p=0.708	p=0.7419
Neutrophil/lymphocyte ratio	r=–0.2698	r=0.1644	r=–0.1752
	p=0.1228	p=0.3942	p=0.3634
Erythrocyte sedimentation rate	r=–0.3295	r=0.00741	r=–0.1099
	p=0.0809	p=0.9720	p=0.6011

mised in the SSc group. Mitral A velocity, E wave deceleration time and E/Em ratio were increased and mitral E/A ratio, lateral and medial annular Em velocity were significantly decreased in SSc patients (Table 4). There was no correlation between stiffness index and inflammation markers (Table 5). Pearson's correlation analysis revealed a significant correlation between mitral E/Em ratio and aortic strain, aortic stiffness index and aortic distensibility in SSc patients (r=−0.2642, p=0.0179, confidence interval [CI]=−0.4574 - −0.04722; r=0.6250, p<0.0001, CI: 0.3964-0.7807 and r=−0.2889, p=0.0119, CI=−0.4841 - −0.0663; respectively). No significant correlation was found between the Medsger severity score and stiffness index (r=0.02543, p=0.8865).

DISCUSSION

We found decreased strain and distensibility and increased aortic stiffness in patients with SSc. In most connective tissue diseases, the relationship between the autoimmune disorder and atherosclerosis is well recognized, as is the fact that this association leads to increased cardiovascular morbidity and mortality. Microvascular disease is a prominent feature of SSc and leads to Raynaud's phenomenon, pulmonary arterial hypertension, and scleroderma renal crisis. The presence of macrovascular disease is less well-established. Proposed mechanisms of the vasculopathy of SSc that have also been implicated in atherosclerosis include endothelial dysfunction, a reduced number of circulating endothelial progenitor cells, and an increased number of microparticles. Excess cardiovascular risk in SSc is suggested by increased arterial stiffness and carotid intima thickening and reduced flow-mediated dilatation (FMD).[12] Although macrovascular disease was not originally considered a feature of SSc, multiple studies have revealed an increased prevalence of large-vessel disease of the upper and lower limbs in patients with

SSc.[6,13] Involvement of great vessels like pulmonary arteries is also proved in addition to the well-known microvasculatory destructive and proliferative pathological process.[3] Accordingly, evaluation of the elastic properties of the aorta became the center of interest for physicians. Several previous studies have researched this issue using various methods. Andersen et al.[7] investigated the relationship between endothelium-dependent and endothelium-independent factors and the stiffness of conduit arteries, as well as levels of endothelial activation markers in patients with SSc. They used the maximum increase in systolic pressure per unit of time (dP/dt[max]), assessed in the radial artery by pulse applanation tonometry as a measure of arterial wall stiffness. The ability of the brachial arteries to dilate in response to hyperemia and nitroglycerin challenge was preserved in SSc and stiffness of the radial artery was found to be increased in this study. The ERAMS study, a multicenter, prospective trial, determined stiffness by another method, namely ambulatory measurement of the QKd interval, which is the time between onset of the QRS wave on the electrocardiogram and detection of the last Korotkoff sound during auscultatory measurement of blood pressure.[9] This study did not show any relationship between arterial rigidity and prognosis at the end of a 1-year follow-up. However, when the study was completed at the end of 3 years, it revealed that a severe progression was predicted by the QKd interval.[14] Moyssakis et al.[15] determined aortic stiffness non-invasively by aortic distensibility and aortic strain measurements. The results of this study presented that stiffness of the aorta is increased in patients with established SSc regardless of the extent of the inflammatory fibrotic process in the skin and lungs, suggesting that additional pathogenetic mechanisms may contribute to the compromise of large arteries. Another method for identification of stiffness, measurement of augmentation index (AI) and pulse wave velocity (PWV) of the brachial artery, was carried out in another study and revealed that increased AI and PWV of the aorta in comparison to age- and sex-matched healthy controls indicate increased large-vessel stiffness in patients with SSc.[16] Similarly, Cypiene et al.[17] designed a study to determine if carotid-radial PWV, aortic AI and endothelial function were altered in SSc patients. PWV and AI were assessed non-invasively by applanation tonometry. The endothelium-dependent FMD test in the brachial artery was performed by an ultrasound system. SSc patients had increased AI and PWV and lower FMD as compared to control subjects. These studies focused on different arteries and used various methods for measurements, and similar results were reported regarding the elastic properties of arteries. Several recent studies also revealed similar outcomes.[18-21] On the other hand, conflicting results have also been reported. Liu et al.[22] demonstrated that there were no differences between study and control groups in the stiffness index and other elasticity parameters when all vessels are considered, and when assessed individually, macrovasculopathy occurs preferentially at the forearm and aorta in SSc. In our study, we evaluated the elastic properties of the aorta in 40 patients with SSc and 38 healthy subjects. Aortic strain, aortic stiffness and aortic distensibility were assessed by transthoracic echocardiography, which is a widely-available and non-invasive tool. Because increased cardiovascular morbidity and mortality was attributed especially to macrovascular changes and flow dynamics, which are assigned via parameters like increased arterial stiffness, carotid intima thickening and reduced FMD, further research on the elastic properties of great vessels had to be carried out. We designed this study to focus on the aorta, one of the most important predictors of cardiovascular events, and to contribute to the evidence that the elastic properties of vessels, especially great ones, are altered. . In line with previous reports, we found increased aortic stiffness and decreased aortic strain and distensibility in SSc patients. All other features that are likely to affect elastic parameters were excluded, and the control group consisted of strictly age- and gender-matched individuals. Therefore, the difference between study and control groups may causatively be attributed to the presence of the disease. These outcomes strengthened the evidence on macrovascular involvement in SSc patients.

In addition to arterial stiffening, left ventricular diastolic functions were compromised in the SSc group. These two conditions may co-exist, or increased aortic stiffness may cause left ventricular diastolic dysfunction. Abnormal arterial stiffness may potentially contribute to the development of left ventricular diastolic dysfunction through increased afterload, which may exacerbate sub-endocardial ischemia, impair myocardial relaxation and promote interstitial fibrosis, leading to reduced left ventricular compliance.[23]

Although the importance of inflammation in the pathogenesis of arterial stiffness has been demonstrated in a number of studies,[24] we found no significant correlation between inflammatory markers and aortic stiffness parameters. This may be due to anti-inflammatory and immunosuppressive medications taken by patients. We can also speculate on mechanisms other than inflammation, or the result may be related to the small number of patients.

Lack of a confirmation method like PWV measurements and other methods used in previous studies may be considered as a limitation of the study. On the other hand, a previous report on the same issue, with the same method and similar patient and control group populations has revealed outcomes consistent with our study. Hence, this may not be a substantial determinant for results. An effort was made to exclude flow dynamics by matching groups with similar blood pressure and heart rate measurements, and thus minimalizing the effect of confounding factors. Eventually, aortic strain and distensibility were lower in patients with SSc, and consequently, aortic stiffness as a marker of cardiovascular morbidity and mortality was increased. Another limitation is the relatively small number of the study group.

There is limited information regarding the prevalence of traditional cardiovascular risk factors in SSc. Data obtained from small studies also conflict. On the other hand, it is well known that overall cardiovascular morbidity and mortality is increased in patients with SSc. Since the increase in cardiovascular adverse events cannot be explained only by the conventional cardiovascular risk factors, a more detailed aspect should be provided in current potential determinants of cardiovascular diseases in patients with SSc. The microvascular pathological process is well-established in patients with SSc, but less is known about macrovascular changes and flow dynamics. Our study demonstrated that aortic stiffness is increased in patients with SSc and, in light of the literature, it is well known that macrovascular changes in particular confer excess cardiovascular risk. As long as increased risk of cardiovascular events is attributed to effects of the disease on the macrovascular system, further studies regarding current cardiovascular risk factors such as stiffness, and other hemodynamical parameters, will continue to be the focus of interest.

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Key words: Aortic stiffness; echocardiography; heart failure, diastolic; heart atria/pathology; systemic sclerosis.

Anahtar sözcükler: Aortik sertlik; ekokardiyografi; kalp yetersizliği, diyastolik; kalp atria/patoloji; sistemik skleroz.