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Original Article

Pulmonary hypertension screening in patients with systemic sclerosis, in a tertiary center, in Turkey; a cross-sectional original study

Türkiye'de tersiyer bir merkezde sistemik skleroz hastalarında pulmoner hipertansiyon taraması; kesitsel orjinal çalışma

Hilal Erken PAMUKCU[1], Çağatay TUNCA[1], Cem OZIŞLER[2], Veysel Ozan TANIK[1], Bahar Tekin TAK[3], Saadet Demirtaş INCI[1], Ali Erhan OZDEMIREL[2], Melih PAMUKCU[2], Tolga Han EFE[1],

[1] Dıskapi Yıldırım Beyazit Training and Research Hospital, Cardiology Department, Ankara/TURKEY

[2] Dıskapi Yıldırım Beyazit Training and Research Hospital,, Romatoloji Kliniği, Ankara/ TURKEY

[3] Ankara Bilkent State Hospital, Cardiology Department Ankara/TURKEY

Abstract

Aim: Development of Pulmonary Hypertension (PH) in Systemic Sclerosis (SS) significantly reduces the survival of the disease and early diagnosis and treatment is very important.

The aim of this study was to investigate the presence of PH in patients who were followed and treated by rheumatology clinic with the diagnosis of SS and who did not have a known diagnosis of PH.

Materials and Methods: This cross-sectional study was completed with 51 patients with SS and a control group of 51 volunteers with similar characteristics in terms of gender and comorbidity. Demographic, laboratory and echocardiographic data were recorded.

Results: The median age of the patients with systemic sclerosis was 53 (46-60) years and the control group was 50 (45-55) years. 42 (82.4%) of the SS patients were female and 39 (76.5%) of the control group were female. Right heart catheterization was performed to 3 patients with high pulmonary artery pressure (>40 mmHg) on transthorasic echocardiography. Group 1 PH was diagnosed in two of three patients (3.9%); group 2 PH was diagnosed in one of three patients (1.9%).

Conclusion: In our study, we detected pulmonary hypertension in 5.8% of 51 patients with systemic sclerosis in a tertiary center. Although these patients have undergone PH screening at certain frequencies, it is noteworthy that we achieved this finding. We believe that we have detected patients with pulmonary systolic pressure at the border and showing rapid progression. Our study supports the more frequent screening of SS patients with borderline pulmonary artery pressure elevation.

Keywords: systemic sclerosis; pulmonary hypertension; echocardiography; right heart catheterization

Corresponding author*: Hilal Erken Pamukcu, Dıskapi Yıldırım Beyazit Training and Research Hospital, Cardiology Department, Ankara/TURKEY
Email: hilalerkenn@gmail.com
Received:7.10.2019 Accepted :09.03.2020
ORCİD: 0000-0001-8116-5090
Doi:10.18663/tjcl.630633

Öz

Amaç: Sistemik Sklerozda (SS) Pulmoner Hipertansiyon (PH) gelişimi hastalığın sürvisini önemli ölçüde azaltmaktadır ve erken tanı ve tedavi çok önemlidir. Çalışmamızda SS tanısıyla romatoloji kliniği tarafından takip ve tedavi altında olan ve ve bilinen PH tanısı olmayan hastaların PH varlığı açısından taranması amaçlanmıştır.

Gereç ve Yöntemler: Bu kesitsel çalışmaSS tanısı olan 51 hasta ve cinsiyet ve komorbidite açısından benzer özellikte 51 gönüllüden oluşan kontrol grubuyla tamamlandı. Demografik, laboratuvar ve ekokardiyografik verileri kayıt edildi.

Bulgular: Sistemik skleroz hasta grubunun ortanca yaşı 53 (46-60), kontrol grubunun 50 (45-55) idi. SS hastalarının 42 (%82,4)'si kadın, kontrol grubunun 39 (%76,5)'sı kadın cinsiyetten oluşmaktaydı. Transtorasik ekokardiyografide pulmoner arter basıncı yüksek saptanan (>40 mmHg) 3 hastaya sağ kalp kateterizasyonu yapıldı. İkisinde grup 1 PH (%3,9); birinde grup 2 PH (%1,9) saptandı

Sonuç: Çalışmamızda, tersiyer bir merkezde sistemik skleroz tanısıyla takipli ve tedavi altında olan 51 hastada %5,8 oranında pulmoner hipertansiyon saptamış bulunmaktayız. Bu hastaların belirli sıklıklarla PH taramasından geçirilmiş olmasına rağmen bu bulguya ulaşmamız dikkat çekicidir. Muhtemelen sınırda pulmoner arter basınç yüksekliği olan hızlı progresyon gösteren hastaları saptadığımızı düşünmekteyiz. Çalışmamız, sınırda pulmoner arter basınç yüksekliği olan SS hastalarının daha sık taranması gerektiğini desteklemektedir.

Anahtar kelimeler: sistemik skleroz; pulmoner hipertansiyon; ekokardiyografi; sağ kalp kateterizasyonu

Introduction

Systemic sclerosis (SS) is a systemic disease of unknown with multiple organ and tissue system involvement, skin being the most common target, and results inflammation, vasculopathy and fibrosis. The most differentiating characteristic of the disease is skin fibrosis called scleroderma, however it may also involve internal organs such as the gastrointestinal tract, kidney, lung and heart, therefore it is termed as systemic sclerosis.

Lung involvement is one of the most severe and lethal organ involvement. Pulmonary hypertension (PS) is another lethal complication that is frequent in SS(1). In SS, the incidence of pulmonary arterial hypertension (PAH) is reported to be 10-15% (2-4) and 3 years of survival has been reported in patients with PAH developed(5). Although SS patients with PAH have been known to have poorer treatment response than idiopathic PAH patients, recent studies showed that similar responses can be achieved with aggressive treatment(6,7). Early diagnosis and treatment is critical in SS related PAH and it is recommended to screen the patients for PH in their follow-ups(8).

In our study, we aimed to investigate the presence of PH in patients who were followed and treated in our hospital with the diagnosis of SS and who did not have a known diagnosis of PH.

Material and Methods

This is a cross-sectional study that aims to investigate the presence of pulmonary hypertension in patients who are being treated with systemic sclerosis diagnosis. Fifty-one patients aged 18 years and over who had admitted to Dışkapı Training and Research Hospital and been treated and followed up for at least 3 years by the Rheumatology outpatient clinic with the diagnosis of Systemic Sclerosis were included in the study. SS diagnosis was based on the diagnostic criteria of American College of Rheumatology(9). The control group of the study consisted 51 subjects with similar age and gender. Autoimmune disease, cardiac valve disease, structural, coronary and congenital heart diseases, arrhythmias, active infection, lung disease, thyroid disease, malignancy, kidney failure, liver disease, electrolyte disorders and pregnancy have been determined as exclusion criteria for the formation of SS patient and control groups. SS and control groups were similar in terms of the presence of hypertension, diabetes mellitus, hyperlipidemia. Moreover, patients who had known severe pulmonary involvement and those with prior diagnosis of pulmonary hypertension were excluded from the SS patient group.

Venous blood samples were obtained from peripheral antecubital vein after 10 hours of fasting.

Whole blood count, fasting blood glucose, renal function tests and erythrocyte sedimentation rate and CRP values were tested. In addition, antinuclear antibody (ANA), anticentromere antibody (ACA) and anti SCL70 antibody tests results were also included as retrospective autoimmune antibody tests.

Height and weight measurements of all participants were

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made and body mass indexes were calculated. Diagnosis year, medications used and comorbidities were recorded, and patients were classified in terms of diffuse and limited scleroderma involvement(9).

Informed consent forms were obtained from all patients. Helsinki Declaration was adhered in the study. Approval of the hospital ethical committee was obtained.

Echocardiographic examination

Transthoracic echocardiographic examinations were performed by using a 2.5-5 MHz transducer with Philips iE33 system (Andover, MA, USA) echocardiographic imaging device.

The examination was performed in the left decubitus position by an experienced cardiologist who was blinded to clinical and laboratory characteristics of the participants. Measurements were repeated three times and their average was used. Essential echocardiography parameters like left atrium, left ventricle end-systolic and end-diastolic dimensions, diastolic ventricular septum and diastolic left ventricle posterior wall thickness were measured by using M-mod echocardiography in parasternal long axis view. Left ventricular ejection fraction (EF) was measured from apical 4- and 2-chamber with Modified Simpson's method and their averages were calculated. Procedure was performed in accordance with international recommendations (10).

With the widest area at the end of systole, the right atrium area in apical 4-chamber view was measured by tracing the right atrium endocardium from the lateral of tricuspid annulus to septal annulus, excluding the area between the leaflets and the annulus, inferior and superior caval veins and apendix(11).

Color Doppler was used to evaluate valvular insufficiency. Left ventricular diastolic filling patterns were evaluated, E and A peak flow rates were recorded and deceleration time was calculated by using pulse-flow Doppler examination.

For the evaluation of left ventricular myocardium functions, Em and Am, which are the left ventricular diastolic velocities for diastolic functions, and the S velocity, which is the systolic function indicator, was obtained by placing the sample volume of Doppler on mitral lateral annulus in apical 4-chamber view.

Peak tricuspid flow rate was calculated from apical four-chamber view based on tricuspid insufficiency flow, and using the Bernoulli equiation, the pulmonary artery systolic pressure (PASP) was calculated by adding the estimated right atrium pressure. Tricuspid annular plane systolic change (TAPSE) was obtained by placing the M-mode cursor on the lateral of tricuspid valve annulus.

Pulmonary artery acceleration time was calculated by measuring the time from the beginning of the pulse flow Doppler envelope to the peak flow occurred.

Pulmonary hypertension was defined as PASB >40 mmHg(12) or tricuspid peak flow velocity over 3.4 m/s in echocardiography, or PH verification with right heart catheterization in patients with tricuspid peak flow velocity between 2.8-3.4 m/s and other accompanying echocardiographic findings of pulmonary hypertension(13). In right heart catheterization of these patients, tt was planned to measure the mean pulmonary artery pressure and pulmonary capillary end pressure. In systemic sclerosis, PH can develop due to pulmonary arterial vasculopathy (Group 1 PH), interstitial lung disease (pulmonary fibrosis (Group 3) or due to increased left cardiac filling pressure (i.e. cardiac involvement) (Group 2) and due to pulmonary venoocclusive disease (Group 1)(14).

According to the latest ESC guidelines(13), precapillary pulmonary hypertension was defined as mean pulmonary artery pressure (MPAP) >25 mmHg and pulmonary pulmonary capiller end pressure (PCEP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units (WU). Post capillary pulmonary hypertension was defined as MPAP >25 mmHg and PCEP >15 mmHg and PVR ≤3 WU. For differential diagnosis in the presence of precapillary PH, interstitial lung disease-related PH presence (group 3PH) was also evaluated. For this purpose, in light of previous studies, it was defined with forced vital capacity <70% in respiratory function test and ILD-related findings in the computed thoracic tomography(15,16). Isolated pulmonary arterial hypertension was defined as the detection of precapillary pulmonary hypertension without the findings of overt interstitial lung disease (i.e. those that do not fit the above description). Pulmonary vaso-occlusive disease was defined as the normal arterial end pressure in the presence of radiographic pulmonary edema(17).

Statistical Analysis

Statistical analyses were performed by using SPSS 23.0 (Statistical Package for Windows, Chicago, Illinois, USA). Continuous variables with normal distribution are presented mean±standard deviation, those without normal distribution are presented as median and interquartile range. Categorical data were represented with numbers and percentages. Kolmogorov-Smirnov test was used to determine the normal distribution of the data.

Student t-test or Mann-Whitney U test was used for numerical variables and chi-square test was used for categorical data.

Results

Total of 102 patients, 51 systemic sclerosis patients and 51 healthy subjects, were included in the study. Demographic characteristics and laboratory results of both groups and the overall population are shown in Table 1. The median age of the systemic sclerosis group was 53 (46-60) years and control group was (45-55) years and there was no significant difference between the groups (p=0.182). There were 42 (82.4%) female patients. In the SS group, number and ratio of hypertensive patients was 16 (31.4%) and 18 (35.3%) in the control group (p=0.834). Median erythrocyte sedimentation rate of the SS group was 20 (15-29.7) mm/h and median ESR of the control group was 8 (7-10) and this difference was statistically significant (p<0.001). Median CRP of the SS group was 4.5 (2.6-10.5) mg/dl and median CRP of the control group was 4.5 (2.6-10.5) and the difference was statistically significant (p=0.001).

Clinical and serological features of the systemic sclerosis patients are shown in Table 2. There was diffuse cutaneous involvement in 22 (43.1%) patients and limited cutaneous involvement in 29 (56.9%) patients. The median diagnosis year of the patients was 5 (3-9) years. In SS group ANA positivity ratio was 78.4%, anticentromere antibody positivity was 25.5%, anti=SCL 70 antibody positivity was 17.6%. All patients had cutaneous involvement and 23 patients (62.7%) had Reynaud syndrome. The evaluation of the patients based on their medication revealed that 40 patients (78.4%) had the most frequent hydroxychloroquine use.

Table 1. Basal characteristics of the participants

Parameters	Study population S=102	Systemic sclerosis S=51	Control group S=51	P value
Age, year	52(45-57)	53(46-60)	50(45-55)	0.182a
Female sex, s(%)	81(79.4%)	42(82.4%)	39(76.5%)	0.624b
Hypertension, s(%)	34(33.3%)	16(31.4%)	18(35.3%)	0.834b
Diabetes mellitus, s(%)	10(9.8%)	4(7.8%)	6(11.8%)	0.739b
Hyperlipidemia, s(%)	28(27.5%)	13(25.5%)	15(29.4%)	0.824b
Smoking, s(%)	19(18.6%)	8(15.7%)	11(21.6%)	0.611b
Body mass index, kg/m2	23(22-25)	23(22-24)	23(22-25)	0.914a
Fasting blood glucose, mg/dl	90(87-98)	91(87-98)	89(86-98)	0.506a
Creatinine, mg/dl	0.8(0.72-0.89)	0.82(0.76-0.96)	0.80(0.67-0.88)	0.096a
Hemoglobin, g/dl	13.4(13-14)	13.2(12.2-14.1)	13.5(13.3-13.8)	0.143a
ESR (mm/hour)	12(8-20)	20(15-29.7)	8(7-10)	<0.001b
CRP (mg/dl)	3(2-5.2)	4.5(2.6-10.5)	3(2-4)	0.001b

S=Number, ESR=Erythrocyte sedimentation rate, CRP=C reactive protein
a: Mann Whitney- U test, b: Pearson chi-square

Table 2. Clinical and serological characteristics of patients with systemic sclerosis

Disease class, s (%)	Diffuse cutaneous SS	22(43.1%)
	Limited cutaneous SS	29(56.9%)
Sex	Female sex	42(82.4%)
Diagnosis year (year)	5 (3-9) years	
Autoantibody profile, s (%)	ANA	40(78.4%)
	ACA	13(25.5%)
	Anti SCL 70	9(17.6%)
Organ/system involvement, s (%)	Reynaud phenomenon	32(62.7%)
	Skin	51(100%)
	Lung	5(10.2%)
	Joint	2(3.9%)
	Gout	6(11.8%)
Treatment, s (%)	Hydroxychloroquine	40(78.4%)
	Steroid	17(33.3%)
	Methotrexate	9(17.6%)
	CCB	21(41.2%)
	Acetylsalicylic acid	15(38.4%)
	Azathioprine	5(9.8%)
	Cyclophosphamide	2(3.9%)
	Mycophenolate mofetil	1(2%)

SS= Systemic sclerosis; ANA = Antinuclear antibody; ACA = Anticentromere antibody, CCB=Calcium channel blocker

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Echocardiographic data of SS patients and the control subjects is presented in Table 3. There was no difference between the groups in terms of left ventricular end diastolic diameter and left ventricular end systolic diameter. The comparison of left atrium diameter revealed median left atrium diameter of 3.4 (3.1-3.7) in the SS group and 2.9 (2.9-3.1) in the control group, and the difference was statistically significant (p<0.001).

Table 3. Echocardiographic features of participants

Parameters	Systemic sclerosis N=51	Control group N=51	P value
LVEDD, cm	4.3 ±0.43	4.23 ±0.17	0.117a
LVESD, cm	2.9±0.32	2.9±0.29	0.576a
Left atrium diameter, cm	3.4 (3.1-3.7)	2.9(2.9-3.1)	<0.001b
Septum thickness, cm	0.96±0.13	0.97±0.06	0.924a
Posterior wall thickness, cm	0.94±0.12	0.96±0.07	0.242a
Left ventricular EF, %	60(60-65)	60(60-62)	0.597b
Mitral filling samples			
E (m/s)	0.633±0.193	0.782±0.133	<0.001a
A (m/s)	0.715±0.171	0.586±0.153	<0.001a
E/A	0.931 ±0.357	1.377 ±0.245	<0.001a
Deceleration time (ms)	180(165-218)	180(170-185)	0.778b
Mitral lateral annulus			
E'm peak velocity (cm/s)	9.7±2.9	12.7±2.3	<0.001a
A'm peak velocity (cm/s)	11.1±3.1	9.5±3.0	0.011a
S m peak velocity (cm/s)	9.2±2.3	10.2±1.7	0.016a
E/Em	7±2.8	6.3±1.6	0.179a
Tricuspid regurgitation velocity, m/sn	2.5(2.3-2.7)	2.1(2.0-2.2)	<0.001b
Pulmonary velocity, m/sn	0.84±0.17	0.80±0.08	0.082a
PASB (mmHg)	28(25-30)	25(20-29)	<0.001b
TAPSE, mm	25(23-27)	23(21-26)	0.215b
Pulmonary acceleration time, ms	103.3±22.5	138.3±5.7	<0.001a
Right atrium area, cm2	12.8±2.4	11.9±1.1	0.018a

a: Student's T test ; b: Mann Whitney U test
LVEDD= Left ventricle end-diastolic diameter; LVESD= Left ventricle end-sistolic diameter; EF= Ejection fraction; E=Early diastolic peak velocity; A=Late diastolic peak velocity; E'm=Mitral lateral anulus early diastolic myocardial peak velocity; A'm= Mitral lateral anulus late diastolic myocardial peak velocity; S m=Mitral lateral anulus peak systolic velocity; PASP= Pulmonary artery systolic pressure; TAPSE= Tricuspid annular plan systolic excursion

The evaluation of mitral diastolic filling patterns showed that E/A ratio was 0.931±0.357 in the SS group and 1.377±0.245 in the control group and the difference was statistically significantly lower (p<0.001). In tissue Doppler examination, mitral lateral annulus Em velocity was 9.7±2.9 cm/s and statistically significantly lower than the control group, which was 12.7±2.3 cm/s (p<0.001). E/Em ratio was 7±2.8 in the SS group and 6.3±1.6 in the control group, and the difference was not statistically significant (p=0.179).

Median tricuspid insufficiency peak flow velocity was 2.5 (2.3-2.7) m/s in the SS group and it was statistically significantly higher than 2.1 (2.0-2.2) m/s in the control group (p<0.001). Median pulmonary artery systolic pressure of the SS group was 28 (25-30) mmHg and median pulmonary artery systolic pressure of the control group was 25 (20-29) mmHg and the difference was statistically significant (p<0.001). In the SS group, the median pulmonary acceleration time was 103.3±22.5 ms and it was statistically significantly shorter than the median pulmonary acceleration time of the control group which was 138.3±5.7 ms (p<0.001). Mean right atrium area of the SS group was 12.8±2.4 cm2 and 11.9±1.1 cm2 in the control group, and it was statistically significantly larger in the SS group (p=0.018).

Right heart catheterization was performed for 3 patients who had been detected to have high pulmonary artery pressure. One patient had mean pulmonary artery pressure=32 mmHg; PCEP=8 mmHg, PVR=4 WU, minimal interstitial lung disease finding in the thorax tomography and FVC was >70% in SFT. Therefore, the patient was considered as group 1 PH and endothelium antagonist treatment was started.

Second patient had MPAP=26 mmHg; PCEP=7 mmHg, PVR=4 WU in the right heart catheterization, there was no lung involvement and endothelium antagonist treatment was started.

Third patient had MPAP=26 mmHg, PCEP=15 mmHg, PVR=3 WU in the right heart catheterization, the patient also had accompanyin hypertension, left ventricle hypertrophy and wide left atrium; left ventricular ejection fraction was normal. The patient was considered as diastolic dysfunction-related group 2 pulmonary hypertension.

As a result of our study, pulmonary hypertension ratio verified by right heart catheterization in patients with systemic sclerosis was found to be 5.8%; group 1 PH in two patients (3.9%), group 2 PH in one patient (1.9%).

Discussion

Based on the results of this cross-sectional study, pulmonary hypertension was detected in 5.8% of the study population by randomized cross-sectional screening of patients with systemic sclerosis who were receiving treatment and being follow-up and had no known diagnosis of pulmonary hypertension. These patients had been closely monitored in a tertiary center and pulmonary hypertension was thought to be excluded in them, therefore detecting pulmonary hypertension in three patients is worthy of attention.

The reported prevalence of pulmonary hypertension in systemic sclerosis has ranged from 5%(18) to 30%(19) based on the definition and exclusion criteria used in prior studies. DETECT study was conducted in 62 centers and included total of 466 SS patients from North America, Europe and Asia who had been diagnosed more than 3 years ago and had DLCO<60% in carbonmonoxide diffusion test, and 19% of the patients had group 1 PH, 6% had group 2 PH and 6% had group PH as proved by right heart catheterization(20). However, different than this reference study, in our study, not all patients who had shortness of breath complaint, reduced diffusion capacity in the carbonmonoxide diffusion test or severe pulmonary involvement in the thoracic tomography and been previously evaluated and examined with pulmonary hypertension pre-diagnosis in their rheumatology follow-up visits were included in our study. In our study, patients who were asymptomatic in terms of pulmonary hypertension, complied with their rheumatology follow-up visits and their drug treatment, were included.

Pulmonary involvement is the most serious and mortality-increasing condition in systemic sclerosis. Median survival is 3 years in systemic sclerosis patients with pulmonary arterial hypertension development(5). Although the treatment response is more difficult than that of those with idiopathic PH, early diagnosis and treatment is crucial. 2015 European Cardiology Society/European Respiratory Society PH guidelines recommend annual PH screening for SS patients(13). In our hospital, patients undergo annual echocardiography examination for cardiac involvement and respiratory function tests for pulmonary involvement in the rheumatology clinic. However, detecting 5.8% pulmonary hypertension in a randomized screening of pulmonary hypertension at a random time is worth noting. This may be due to the rapid progression observed in patients with borderline pulmonary artery systolic pressure in echocardiography. In the literature, it has been reported that 42% of the systemic sclerosis patients with MPAP 21-25 mmHg in right heart catheterization experienced PH development after MPAP increased over 25 mmHg after a second catheterization during median 48-month follow-up(21), and that the possibility of overt PAH development is higher in patients with borderline MPAP at the time diagnosis in comparison to the those with MPAP 20 mmHg. Borderline SPAP may have been detected in previous echocardiography of the patients who were found to have PH in our study. This result supports the notion that systemic sclerosis patients with borderline arterial pressure should be monitored more frequently.

Types of pulmonary hypertension that can be seen in systemic sclerosis are group 1 pulmonary HT that occurs due to vasculopathy in small pulmonary arteries, group 3 PH that is related to interstitial lung disease and hypoxia, and group 2 pulmonary hypertension which occurs due to systolic and diastolic dysfunction as a result of myocardial fibrosis. In addition, pulmonary veno-occlusive disease is not rare and can be a cause of PH in SS patients (14). Several of these mechanisms may be the cause of PH together in the same patient and its differentiation can be difficult in clinical practice. Isolated Group 1 PH is generally the most common type (14). In the DETECT study, 60% of the patients with PH were Group 1 PH, 20% were Group 2 PH, 20% were Group 3 PH (lung disease/hypoxia). In our study, pulmonary hypertension was detected in 3 patients, two of them were Group 1 and one was Group 2, and one of the patients in Group 1 PH was considered as such since interstitial pulmonary involvement was minimal.

In our study, diastolic functions of the SS group was found to be significantly more deteriorated than the control group. In SS, systolic and/or diastolic dysfunction may be related to fibrosis, left

ventricular hypertrophy, hypertension and renal disease(22,23).

As hypertension, age and diabetes mellitus presence, factors that can affect the diastolic functions, were similar between the groups, we believe that this finding is associated with systemic sclerosis-related fibrosis; diastolic dysfunction in systemic sclerosis is not rare according to literature(24), cardiac involvement starts with diastolic dysfunction.

Subtypes of systemic sclerosis are generally classified as diffuse cutaneous and limited cutaneous(25). This classification is associated with skin involvement and independent from organ involvement. However, organ involvement can be more frequent and onset earlier in SS patients with diffuse involvement(26). The only exception is that pulmonary arterial hypertension can be equally frequent in both diffuse and limited cutaneous involvement(27). Two group 1 PH patients were determined have diffuse cutaneous type and one Group 2 PH patients had limited cutaneous type. In our study, we were unable to make an association between skin involvement and PH presence as we had few number of patients with PH.

In our study, we used echocardiographic evaluation for PH screening and the parameters like carbonmonoxide diffusion test, NTproBNP, which were included in the DETECT algorithm(20), were not evaluated, however, our study plan was different than the previous PH screening studies. In our study, SS patients who had been evaluated and thought to be excluded in terms of PH in their rheumatology follow-up visits were evaluated in terms of pulmonary hypertension. The studies involving PH screening in systemic sclerosis studies conducted a broader evaluation within a wider timeframe and unlike our study, all patients who had been evaluated in rheumatology visits were included in the studies(18,19). Therefore, the prevalence of PH may be higher in these previous studies. In another study, it was reported that patients with DLCO≥80% may still have PH(28). In our patients detected with PH, we believe that PH may be excluded in rheumatologic follow-up in a similar way.

Limitation of the study

We believe that the cross-sectional design of our study was a limitation. A prospective study where SS patients are followed up and incidence of PH is determined in addition to its prevalence could have been more valuable. Due to our study design, we were unable to access the previous echocardiography and other examinations in rheumatology follow-up and therefore could not evaluate the rate and duration of PH development. The PASP 40 mmHg threshold value for the right heart catheterization indication may be a high threshold and therefore the prevalence of PH could be lower than its actual value.

Conclusion

In our study, we detected pulmonary hypertension in 5.8% of 51 patients who have been treated and monitored with systemic sclerosis diagnosis in a tertiary center. Two of these three patients were in 1 PH class and one was in 2 PH class. It is noteworthy that we have detected PH in patients who had been closely monitored, screened for pulmonary HT in their follow-up visits and thought to be excluded in terms of PH. We believe that our study supports the notion that the presence of pulmonary hypertension, a serious condition that significantly increases morbidity and mortality in systemic sclerosis, should be evaluated with more detailed algorithms and that especially the patients with borderline pulmonary artery systolic pressure should be more closely monitored.

Declaration of conflict of interest

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References

1. Le Pavec J, Launay D, Mathai SC, Hassoun PM, Humbert M. Scleroderma lung disease. Clinical reviews in allergy & immunology 2011;40:104-16.
2. Steen V, Chou M, Shanmugam V, Mathias M, Kuru T, Morrissey R. Exercise-induced pulmonary arterial hypertension in patients with systemic sclerosis. Chest 2008;134:146-51.
3. Yang X, Mardekian J, Sanders KN, Mychaskiw MA, Thomas J, 3rd. Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a systematic review of the literature. Clinical rheumatology 2013;32:1519-31.
4. Hachulla E, Gressin V, Guillevin L et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis and rheumatism 2005;52:3792-800.
5. Lefevre G, Dauchet L, Hachulla E et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis and rheumatism 2013;65:2412-23.
6. Coghlan JG, Galie N, Barbera JA et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. Annals of the rheumatic diseases 2017;76: 1219-27.

7. Gaine S, Chin K, Coghlan G et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. The European respiratory journal 2017;50.
8. Simonneau G, Montani D, Celermajer DS et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. The European respiratory journal 2019;53.
9. van den Hoogen F, Khanna D, Fransen J et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/ European League against Rheumatism collaborative initiative. Arthritis and rheumatism 2013;65:2737-47.
10. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2015;28:1-39
11. Rudski LG, Lai WW, Afilalo J et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2010;23:685-713.
12. Meune C, Avouac J, Wahbi K et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: A controlled study of 100 consecutive patients. Arthritis and rheumatism 2008;58:1803-09.
13. Galie N, Humbert M, Vachiery JL et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). The European respiratory journal 2015;46:903-75.
14. Launay D, Sobanski V, Hachulla E, Humbert M. Pulmonary hypertension in systemic sclerosis: different phenotypes. European respiratory review : an official journal of the European Respiratory Society 2017;26.
15. Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. Annals of the rheumatic diseases 2006;65:1336-40.
16. Kowal-Bielecka O, Avouac J, Pittrow D et al. Echocardiography as an outcome measure in scleroderma-related pulmonary arterial hypertension: a systematic literature analysis by the EPOSS group. The Journal of rheumatology 2010;37:105-15.
17. Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. American journal of respiratory and critical care medicine 2000;162:1964-73.
18. Avouac J, Airo P, Meune C et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. The Journal of rheumatology 2010;37:2290-98.
19. McGoon MD, Benza RL, Escribano-Subias P et al. Pulmonary arterial hypertension: epidemiology and registries. Journal of the American College of Cardiology 2013;62:51-59.
20. Coghlan JG, Denton CP, Grunig E et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Annals of the rheumatic diseases 2014;73:1340-9.
21. Valerio CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Arthritis and rheumatism 2013;65:1074-84.
22. Champion HC. The heart in scleroderma. Rheumatic diseases clinics of North America 2008;34:181-90
23. Parks JL, Taylor MH, Parks LP, Silver RM. Systemic sclerosis and the heart. Rheumatic diseases clinics of North America 2014;40:87-102.
24. Roque MCF, Sampaio-Barros PD, Arruda AL et al. Evaluation of Left Ventricular Diastolic Function by Echocardiography with Tissue Doppler in Systemic Sclerosis. Arquivos brasileiros de cardiologia 2017;109:410-415.
25. LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. The Journal of rheumatology 2001;28:1573-76.
26. Hachulla E, Launay D. Diagnosis and classification of systemic sclerosis. Clinical reviews in allergy & immunology 2011;40:78-83.
27. Hachulla E, de Groote P, Gressin V et al. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis and rheumatism 2009;60:1831-39.
28. Young A, Nagaraja V, Basilious M et al. Update of screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension. Seminars in arthritis and rheumatism 2019;48: 1059-67.