

Evaluation of pulmonary artery stiffness in patients with systemic sclerosis

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ABSTRACT

Objective: The study aims to investigate the use of pulmonary artery stiffness (PAS) parameter in early diagnosis of systemic sclerosis (SSc) and pulmonary hypertension in SSc patients.

Patients and Methods: The study involved 102 SSc patients and 45 control group patients, who underwent transthoracic echocardiographic evaluations.

Results: Pulmonary artery stiffness was measured as 25.7 ± 7.6 (Hz/msn) in the SSc cases and 13.7 ± 1.6 (Hz/msn) in the healthy subjects ($P < 0.001$). TAPSE/sPAP ratio, which we used as an indicator of RV-PA coupling, was calculated as 0.65 ± 0.28 in SSc cases and 1.12 ± 0.33 in the control group ($P < 0.001$).

When we evaluated PAS values of subgroups PAS was significantly higher in SScPH(-) patients without pulmonary hypertension than control subjects (respectively; 21.67 ± 3.9 ; 13.7 ± 1.6 , $P < 0.001$). The relationship of PAS with the parameters in which pulmonary hypertension and right ventricular functions were evaluated, there was a positive correlation with sPAP ($r = -0.396$, $P < 0.001$), while a negative correlation was observed with TAPSE/sPAP ($r = 0.456$, $P < 0.001$).

Conclusion: We observed higher PAS values in SScPH(-) patients compared to the control group and found a positive correlation between the increase in PAS and sPAP and a negative correlation between them and TAPSE/sPAP.

Keywords: Pulmonary hypertension, Systemic sclerosis, Transthoracic Echocardiography, Pulmonary arterial stiffness, TAPSE/sPAP ratio

1. INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by multi-organ involvement. It leads to increased morbidity and mortality depending on the degree of organ involvement. Pulmonary involvement most commonly leads to pulmonary hypertension (PH) and interstitial lung disease. The incidence of pulmonary hypertension in SSc patients is between 8-12% [1]. Several mechanisms exist for the development of pulmonary hypertension. According to the latest pulmonary hypertension guideline, it may be in the group of connective tissue-related pulmonary arterial hypertension (PAH) (Group 1.4.1) or in the group of lung-associated pulmonary hypertension (Group 3) due to interstitial lung disease [2].

Patients who develop PH may present with symptoms such as asymptomatic or shortness of breath. Many scoring systems have been developed for the early detection of PH development and

the most commonly used one is the DETECT algorithm. This algorithm is a simple and reliable tool for PAH detection in SSc [3]. According to this algorithm, transthoracic echocardiography stands out as the first test to be screened.

Myocardial involvement in SSc causes fibrosis and impaired microcirculatory function [4]. The worsening morbidity and mortality of SSc-PAH compared with other PH cases may be partially related to inadequate compensation of the right ventricle due to increased afterload. The inability of the right ventricle to cope with SSc-PAH leads to an inadequate link between right ventricular contractile function and increased pulmonary afterload due to PAH. This results in deterioration of the right ventricle to pulmonary artery (RV-PA) coupling.

Transthoracic echocardiography (TTE) has a crucial role in the diagnosis and screening strategy of PH [5]. Ultrasonographic evaluation of the RV and pulmonary vascular bed is very useful

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to identify detectable pathological changes in the pulmonary circulation in the early stage of the disease. As a determinant of pulmonary vascular bed functions, pulmonary arterial stiffness (PAS) can be measured echocardiographically [6].

In our study, we aimed to investigate whether we can use the PAS parameter to predict the development of PH and deterioration in RV-PA coupling early in SSc patients.

2. PATIENTS and METHODS

The study was undertaken at Marmara University, Pendik Training and Research Hospital, a tertiary center for echocardiography laboratory. A local ethical committee approval was obtained, and the study was undertaken in accordance with the declaration of Helsinki. Consecutive SSc patients who applied to our outpatient clinic between January 2017 and January 2023 were included in the study retrospectively. The SSc diagnoses of the patients were set to meet the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classifications during their follow-up in the Rheumatology Department of our hospital [7]. Exclusion criteria were hemodynamically significant valvular disease (any stenosis and/or regurgitation greater than mild in severity), coronary artery disease (documented coronary atherosclerosis, segmental wall motion abnormality, history of myocardial infarction), ischemic, dilated or hypertrophic cardiomyopathy, pulmonary embolism, evidence of intracardiac shunting or congenital heart disease and poor echocardiographic images. The control group included 45 consecutive age and gender-matched individuals who were referred for echocardiography from the Cardiology Outpatient Clinic at the discretion of their physician over the study period. Baseline clinical properties, such as age, gender, and body mass index (BMI) and laboratory findings were recorded. Skin, lung and other organ involvements of the patients were evaluated in terms of SSc involvement. Diffusing capacity of the lungs for carbon monoxide (DLCO) test was performed for respiratory functions.

TTE evaluation

In this research, TTE was performed by two experienced echocardiographers who were unaware of the patients' medical data. For all measurements an Epiq 7 system (Philips Medical Systems, Andover, MA, USA) equipped with a 3.5 MHz transducer (S5-1 probe) were applied. The American Society of Echocardiography's recommendations for conventional echocardiographic measurements were followed [8]. Modified biplane Simpson's method was used to determine left ventricular ejection fraction (LVEF) [8]. In order to record either mitral or tricuspid flow velocities, the sample volume was oriented at the tip of both valve leaflets in an apical four-chamber window by applying the pulsed-Doppler method. The sample volume was positioned in the apical four chamber window either on the mitral lateral annulus or the tricuspid lateral annulus to acquire the LV and right ventricle (RV) tissue Doppler variables using the pulsed-wave Doppler method. The RV myocardial performance index (MPI) was calculated using the following equation: tricuspid valve closure to opening time RV – ejection time (ET)

/RV-ET [8]. RV mid and annular diameters were obtained at the end-diastole from the apical four-chamber window. The RV annular segment's systolic motion across the lateral free wall of the tricuspid annulus in the apical four-chamber view was seen using M-mode imaging, and this motion was used to measure the tricuspid annular plane systolic excursion (TAPSE). The diameter and collapsibility of the inferior vena cava and the tricuspid regurgitant velocity were used to calculate the systolic pulmonary artery pressure (sPAP). RV-fractional area change (FAC) is calculated that distinction between RV end-diastolic and end-systolic areas measured through ideally RV-focused apical view [8]. RV – PA coupling was calculated according to the following formula: TAPSE /sPAP and when a ratio <1.6 was obtained, it was characterized as impaired coupling [9].

Pulmonary Hypertension Definition in Echocardiographic Parameters

Regardless of the underlying etiology, PH causes right ventricular pressure overload and dysfunction, which can be detected by echocardiography. Echocardiography is also a valuable tool in identifying suspected or confirmed causes of PH. However, echocardiography alone is not sufficient to confirm the diagnosis of PH, and right heart catheterisation (RHC) is required. Given the heterogeneous nature of PH and the unique geometry of the RV, there is no single echocardiographic parameter that reliably provides insight into the condition and underlying etiology of PH. Therefore, comprehensive echocardiography when PH is suspected includes estimation of sPAP and identification of additional signs suggestive of PH, with the aim of assigning an echocardiographic grade to the probability of PH.

Estimates of sPAP are based on peak tricuspid regurgitation velocity (TRV) and TRV-derived tricuspid regurgitation pressure gradient (TRPG) after excluding pulmonary artery stenosis, and are based on the non-invasive measurement of RA pressure (RAP). Given the inaccuracy of RAP estimation and the amplification of measurement error through the use of derived variables, the key variable for assigning echocardiographic PH probability is peak TRV (and not estimated sPAP). Peak TRV at 0.2.8 m/s may indicate PH. However, TRV alone cannot reliably determine the presence or absence of PH. Therefore, additional variables related to RV morphology and function can be used to define the echocardiographic probability of PH, which can be determined as low, intermediate, or high.

Right ventricular outflow tract acceleration time (RVOT) is measured from flow onset to peak flow rate. Since the objective is to assess the time to reach peak velocity, not diffusion, it is important to first place the marker at the peak and then work back to the beginning of the flow. Results greater than 130 ms are considered normal, whereas results less than 100 ms are highly suggestive of pulmonary hypertension. The formula for calculating mean pulmonary pressure is $mPAP = 90 (0.62 \cdot AT_{RVOT})$.

Measurement of Pulmonary Arterial Stiffness

We first found the pulmonary artery in the parasternal short-axis window. The semilunar pulmonic valve was then exposed for the Doppler recordings of pulmonary blood flow. For at least 5 subsequent beats, the pulmonary flow's maximum frequency shift (MFS) was recorded. Pulmonary flow acceleration time (PfAT) was recorded for at least five subsequent beats and is defined as the interval between the beginning of SPA flow and peak flow rate. Next, the average MFS and average PfAT were divided to yield the PAS value [10] (Figure 1).

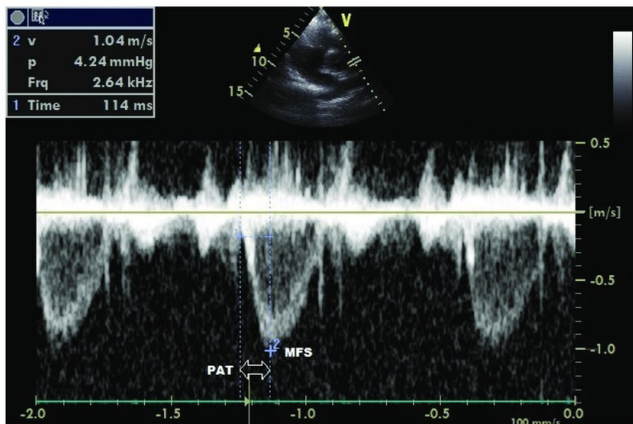


Figure 1. An illustration of a patient showing PAS measurement. PAS indicates pulmonary artery stiffness, PfAT indicates pulmonary flow acceleration time, and MFS indicates maximum frequency shift

Statistical Analysis

For all analyses, SPSS (version 26.0; SPSS Inc., Illinois, USA) statistical software was used. Continuous variables were expressed as mean \pm standard deviation (SD). Categorical variables were expressed as numbers (percentage). The Kolmogorov-Smirnov test was used to determine if continuous variables are normally distributed. SSc and the control group were compared using independent variables by the chi-square, Fischer's exact test, Student's *t* test, Man-Whitney *U*, and Kruskal-Wallis tests, if necessary. SSc PH(+), SSc PH(-) and the control groups were compared using independent variables using ANOVA test. To assess the correlation between PAS and the right ventricular echocardiographic parameter, we applied a Pearson correlation test. For all statistics, a P value below 0.05 was considered significant.

3. RESULTS

Initially, 114 SSc patients were included in the study. Twelve patients were excluded from the study due to inadequate echocardiographic image (n:6), history of coronary artery disease (n: 2), and moderate-to-advanced valve insufficiency (n:4). According to the rheumatological examinations of SSc patients, skin involvement was found in 72 patients and lung involvement (interstitial lung disease) was found in 46 patients. Patients were classified as limited cutaneous SSc (lcSSc, n = 45) or diffuse form (dcSSc, n = 27) according to the degree of skin involvement. 32 SSc patients were

classified as SSc PH (+) if they had tricuspid regurgitant velocity $>$ 2.8 m/s along with further echocardiographic PAH signs. PH(-) was assigned to the remaining patients (70 SSc with tricuspid regurgitation velocity $<$ 2.8 m/s and no other echocardiographic PH signs). The functional capacity of all patients was 1-2. Electrocardiographic evaluations of the patients were performed. Atrial fibrillation was detected in 8 of the patients, frequent supraventricular premature beats in 4 patients, and frequent ventricular extra beats were detected in 5 patients. In the other patients, including the control group, all were in sinus rhythm, and no specific findings of right ventricular hypertrophy or dilatation were observed. In the rheumatological evaluation of the patients, antiScl antibody was detected positive in 38 patients, while ANA was negative in 41 patients. This information was also added to the results section. All 32 PH patients were using endothelin receptor antagonists, and 11 were also taking phosphodiesterase inhibitors. Inhalers (27 individuals), methotrexate (10 patients), azathioprine (11 patients), danasumab (4 patients), hydroxychloroquine (55 patients), and mycophenolate mofetil (25 patients) were among the drugs taken by the patients. In terms of basic characteristics, no statistical difference was found between the groups which were shown in Table I. Only N-terminal pro-brain natriuretic peptide (NT-proBNP) was found to be significantly higher in the SSc group than in the control group.

Table I. Baseline characteristics*

	Systemic Sclerosis (n=102)	Control group (n=45)	P value
Age, years	54.7 \pm 13.2	56.4 \pm 10.2	0.567
Female, n (%)	81 (79)	34 (76)	0.782
BMI, kg.m ⁻²	27.4 \pm 4.4	28.1 \pm 3.7	0.686
Heart rate, beats.min ⁻¹	82.1 \pm 13.9	77.7 \pm 12.1	0.435
SBP, mmHg	120.1 \pm 17.7	124.9 \pm 12.4	0.259
Comorbidities			
Hypertension, n (%)	61 (60)	28 (62)	0.543
Diabetes, n (%)	24 (23)	10 (22)	0.897
Dyslipidemia, n (%)	19 (18)	9 (20)	0.321
Functional status			
WHO class I, n (%)	76 (75)	45 (100)	
WHO class II, n (%)	26 (25)	-	
WHO class III, n (%)	-	-	
WHO class IV, n (%)	-	-	
Laboratory parameters			
Creatinin, mg.dL ⁻¹	0.73 \pm 0.2	0.66 \pm 0.14	0.076
Hemoglobin, g.dL ⁻¹	12.6 \pm 1.7	13.5 \pm 1.68	0.856
CRP, mg.L ⁻¹	7.1 \pm 22.1	6.1 \pm 14.3	0.879
hs-cTnT, ng.L ⁻¹	9.8 \pm 8.2	5.6 \pm 3.9	0.032
NT-proBNP, ng.L ⁻¹	448.1 \pm 823.9	51.7 \pm 47.7	0.008
DLCO	74.8 \pm 23.6	-	-

*Values are mean \pm standard deviation, number (percentage). BMI: body mass index, CRP: C-reactive protein, DLCO: diffusing capacity of the lungs for carbon monoxide, hs-cTnT: high-sensitivity cardiac troponin T, NT-proBNP, N-terminal pro-brain natriuretic peptide, SBP: systolic blood pressure, WHO: World Health Organization.

Echocardiographic parameter results are summarized in Table II. No significant differences were detected in LV diameters and LVEF between the groups. RA and LA areas were higher in SSc patient. Mitral E, A was higher in SSc patients, E/e' were not different between groups. RV/LV ratio was significantly shorter in control patients. RV TDI parameters were impaired in SSc patients. Although, RVFAC, TAPSE, and RVs' were shorter in SSc patients, RV-MPI was similar between groups. SSc patients had significantly higher sPAP and shorter pulmonary acceleration time.

Pulmonary arterial stiffness was measured as 25.7 ± 7.6 (Hz/msn) in the SSc cases and 13.7 ± 1.6 (Hz/msn) in the healthy subjects ($p < 0.001$). TAPSE/sPAP ratio, which we used as an indicator of RV-PA coupling, was calculated as 0.65 ± 0.28 in SSc cases and 1.12 ± 0.33 in the control group ($P < 0.001$).

Table II. Echocardiographic parameters*

	Systemic Sclerosis (n=102)	Control group (n=45)	P value
Echocardiographic parameters			
LVEF, %	61.4 ± 4.8	60.9 ± 2.7	0.565
LVEDd, mm	44.7 ± 4.7	43.9 ± 4.6	0.343
IVSd, mm	9.5 ± 1.7	9.6 ± 2.1	0.545
RA area, cm ²	16.1 ± 4.3	13.3 ± 2.2	<0.001
LA area, cm ²	16.5 ± 4.1	14.5 ± 2.1	0.002
E _{Mp} , cm/s	0.88 ± 0.24	0.78 ± 0.16	0.03
A _{Mp} , cm/s	0.83 ± 0.19	0.71 ± 0.14	0.001
E/e' _M	9.2 ± 3.2	9.1 ± 3.1	0.894
RV mid, mm	38 ± 5.6	28.9 ± 2.29	0.007
RV annular, mm	44.1 ± 5.4	34.9 ± 1.7	<0.001
E _r , cm/s	0.79 ± 0.7	0.59 ± 0.15	0.023
A _r , cm/s	0.74 ± 0.89	0.47 ± 0.09	0.005
RVs', cm/s	12.4 ± 2.8	13.3 ± 1.7	0.027
RV/LV	0.75 ± 0.19	0.68 ± 0.09	0.024
TR V _{max} , m.sec ⁻¹	2.79 ± 0.65	2.05 ± 0.4	<0.001
sPAP, mmHg	38.7 ± 17.1	21.9 ± 6.1	<0.001
mPAP, mmHg	22.4 ± 10.2	14.3 ± 3.5	0.002
RV MPI	0.33 ± 0.04	0.31 ± 0.06	0.124
RV FAC, (%)	46.9 ± 17.9	67.8 ± 16.4	<0.001
PAd, mm	19.6 ± 5.1	19.2 ± 2.2	0.734
PfAT, msn	110.6 ± 18.5	155.1 ± 14.9	<0.001
MFS, Hz	2730 ± 424	2122 ± 172	<0.001
PAS, Hz. msn ⁻¹	25.7 ± 7.6	13.7 ± 1.6	<0.001
TAPSE, mm	20.1 ± 3.6	24.5 ± 2.7	<0.001
TAPSE/sPAP, mm.mmHg ⁻¹	0.65 ± 0.28	1.12 ± 0.33	<0.001
IVC, mm	16.8 ± 5.3	12.7 ± 3.2	0.002

* Values are mean ± standard deviation or number (percentage).

AM: mitral flow A-wave, AT: tricuspid flow A-wave, EM: mitral flow E-wave, ET: tricuspid flow E-wave, e': tissue Doppler e' wave, IVC: inferior vena cava diameter, FAC: fractional area change, IVS: interventricular septum thickness, LA: left atrium, LVEDD: left ventricle end-diastolic diameter, LV: left ventricle, LVEF: left ventricle ejection fraction, MFS: maximum frequency shift, PAd: pulmonary artery diameter, PAS: pulmonary arterial stiffness, PfAT: pulmonary flow acceleration time, RV annular: right ventricle annular diameter, RV mid: right ventricle midregion diameter, RV MPI: right ventricle myocardial performance index, RV s': tricuspid anulus systolic velocity, mPAP: mean pulmonary arterial pressure, sPAP: systolic pulmonary arterial pressure, TR Vmax: tricuspid regurgitation maximal velocity, TAPSE: tricuspid annular plane systolic excursion.

When we evaluated PAS values of subgroups (SSc patients with and without pulmonary hypertension and control subjects), PAS was significantly higher in SSc patients with pulmonary hypertension than SSc patients without pulmonary hypertension (respectively; $n = 32$, mean = 34.6 ± 5.9 ; $n = 37$, mean = 21.67 ± 3.9 ; $P = < 0.001$). Moreover PAS was significantly higher in SScPH (-) patients without pulmonary hypertension than control subjects (respectively; $n = 70$, mean = 21.67 ± 3.9 ; $n = 45$, mean 13.7 ± 1.6 , $P < 0.001$).

In the analysis performed by separating SSc patients according to whether they have pulmonary hypertension or not, the sPAP, PAS, RV-MPI values were significantly higher in the group with pulmonary hypertension, while RV-FAC, PfAT and TAPSE/sPAP ratios were significantly lower (Table III).

Table III. Comparison of conventional echocardiography variables of the patients with systemic sclerosis according to the presence or absence of pulmonary arterial hypertension

	Systemic Sclerosis PH (-) (n=70)	Systemic Sclerosis PH (+) (n=32)	Control group (n=45)	p value
Echocardiographic parameters				
PfAT, msn	118.2 ± 14.3	92.7 ± 13.2	155.6 ± 14.9	<0.001
MFS, Hz	2541 ± 329	3143 ± 296	2122 ± 172	<0.001
PAS, Hz/msn	21.6 ± 3.9	34.6 ± 5.9	13.7 ± 1.6	<0.001
TR V _{max} , m.sec ⁻¹	2.42 ± 0.36	3.48 ± 0.6	2.05 ± 0.4	<0.001
mPAB, mmHg	19.9 ± 4.8	31.2 ± 10.6	15.4 ± 3.7	0.009
RV MPI	0.26 ± 0.99	0.42 ± 0.13	2.6 ± 9.9	<0.001
RVFAC, %	50.5 ± 17.4	38.6 ± 15.8	67.8 ± 16.4	<0.001
PAd, mm	3.85 ± 0.8		4.23 ± 0.69	0.001
TAPSE, mm	21.9 ± 2.6	16.7 ± 2.9	24.5 ± 7.7	<0.001
TAPSE/sPAP, mm.mmHg ⁻¹	0.82 ± 0.26	0.38 ± 0.14	1.12 ± 0.33	<0.001
E _r , cm/s	0.86 ± 1.2	0.97 ± 1.3	0.59 ± 0.15	0.536
A _r , cm/s	0.72 ± 1.03	1.04 ± 1.5	0.47 ± 0.09	0.186
RVe', cm/s	11.9 ± 2.6	10.2 ± 2.6	11.8 ± 3.3	0.014
RVa', cm/s	12.5 ± 3.8	11.1 ± 2.8	16.1 ± 3.8	<0.001
RVs', cm/s	12.8 ± 2.7	11.4 ± 2.9	13.7 ± 1.7	0.003
IVC, mm	15.6 ± 4.6	19.8 ± 5.5	12.7 ± 3.2	0.032

* Values are mean ± standard deviation.

AT: tricuspid flow A-wave, a': tissue Doppler a', ET: tricuspid flow E-wave, e': tissue Doppler e' wave, IVC: inferior vena cava diameter, FAC: fractional area change, MFS: maximum frequency shift, PAd: pulmonary artery diameter, PAS: pulmonary arterial stiffness, PfAT: pulmonary flow acceleration time, RV MPI: right ventricle myocardial performance index, RV s': tricuspid anulus systolic velocity, Mpap: mean pulmonary arterial pressure, TR Vmax: tricuspid regurgitation maximal velocity, TAPSE: tricuspid annular plane systolic excursion.

When the patients were separated according to whether the RV-PA coupling was impaired or not, the sPAP, PAS and RV-MPI values were significantly higher in the impaired group, while RV-FAC, PfAT and TAPSE/sPAP ratios were significantly lower (Table IV).

Table IV. Comparison of conventional echocardiography variables of the patients with systemic sclerosis according to the presence or absence of RV-PA coupling

	RV-PA coupling(-) (n=18)	RV-PA coupling(+) (n=129)	p value
Echocardiographic parameters			
PfAT, msn	121.6±27.1	143.4±16.6	<0.001
MFS, Hz	2215±275	2590±463	<0.001
PAS, Hz/msn	22.9±8.5	15.7±3.4	<0.001
TR V _{max} , m.sec ⁻¹	2.64±0.66	1.82±0.12	<0.001
mPAB, mmHg	23.5±9.9	12.2±1.1	<0.001
RV MPI	0.37±0.12	0.32±0.11	0.041
RVFAC,%	48.4±19.1	62.5±14.8	0.011
PA _d , mm	19.5±4.5	18.9±1.8	0.64
TAPSE, mm	21.1±3.8	25.2±2.6	<0.001
E _p , cm/s	0.76±0.74	1.5±2.9	0.021
A _p , cm/s	0.71±0.84	1.24±2.4	0.114
RV _e , cm/s	11.5±2.9	11.1±1.4	0.654
RV _a , cm/s	12.5±3.8	14.4±4.5	0.113
RV _s , cm/s	12.7±2.7	12.5±2.1	0.826
IVC, mm	14.2±3.8	9.5±5.6	0.049

* Values are mean ± standard deviation

AT: tricuspid flow A-wave, a': tissue Doppler a', ET: tricuspid flow E-wave, e': tissue Doppler e' wave, IVC: inferior vena cava diameter, FAC: fractional area change, MFS: maximum frequency shift, PA_d: pulmonary artery diameter, PAS: pulmonary arterial stiffness, PfAT: pulmonary flow acceleration time, RV MPI: right ventricle myocardial performance index, RV s': tricuspid anulus systolic velocity, mPAP: mean pulmonary arterial pressure, TR V_{max}: tricuspid regurgitation maximal velocity, TAPSE: tricuspid annular plane systolic excursion.

When the relationship of PAS with the parameters in which pulmonary hypertension and right ventricular functions were evaluated, there was a positive correlation with sPAP (r: -0.396, P<0.001), while a negative correlation was observed with TAPSE/sPAP (r: 0.456, P<0.001) (Figure 2).

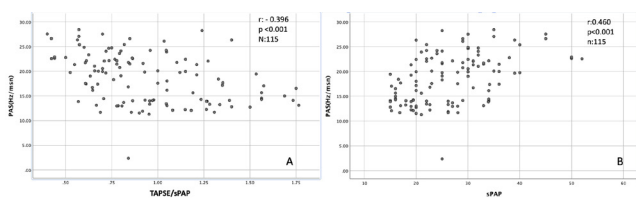


Figure 2. A: Correlation analysis between PAS and TAPSE/sPAP. B: Correlation analysis between PAS and sPAP. PAS indicates pulmonary artery stiffness, TAPSE indicates tricuspid annular plane systolic excursion, and sPAP indicates systolic pulmonary pressure

4. DISCUSSION

To our knowledge, this is the first study indicating higher PAS values in SSc patients. In the present investigation, we observed that SSc patients without PH had higher PAS values than healthy people, which may indicate an early shift in the pulmonary vascular bed among these instances.

The development of pulmonary hypertension has been shown to be the highest risk factor associated with the survival of SSc patients. In a study evaluated for the first time by Koh et al., the 1-year survival rate of PH associated with untreated SSc was approximately 50%; this rate is >90% in patients with lung involvement without PH or without any significant organ involvement [11]. In addition to direct pulmonary artery involvement, right ventricular failure owing to myocardial fibrosis plays a role in the development of pulmonary hypertension. TTEs from PH patients indicate reduced right ventricular systolic and diastolic functioning [12]. In our study, 32 SSc patients had pulmonary hypertension, and we discovered a substantial increase in sPAP values and a significant drop in RV-MPI, RV-FAC, TAPSE, and RVs values. Although, this finding is generally accepted, it is known that deterioration in right ventricular functions begins in the early period in patients who are not found to have PH with conventional echocardiographic parameters. In a study by Demirci et al., SSc patients had lower RV longitudinal strain (RV-LS) and higher right ventricular dyssynchrony (RV-Dys) than controls, although, there was no significant difference in conventional echocardiographic variables related to RV function [13]. In our study, no significant difference was found in conventional echocardiography parameters in SSc patients who did not develop PH compared to the control group, except for PAS.

The pulmonary circulation is a low pressure, low resistance, high distensibility system. The majority of the total vascular bed compliance is located in the proximal arterial branches. Therefore, the predictive value of pulmonary vascular bed compliance in chronic PAH is also related to increased stiffness of the proximal pulmonary artery. PAH is a disease of the small distal pulmonary arteries characterized by vasoconstriction resulting in increased pulmonary vascular resistance (PVR) and, as a result, increased pulmonary artery pressure. Increased pressure causes dilation and stiffness of the proximal pulmonary artery and can also cause remodeling of the vessel wall, which can subsequently influence stiffness. Therefore, both pressure and changes in the vessel wall contribute to proximal pulmonary artery stiffness. Therefore, PAS evaluation may be important in the early diagnosis of PH. PAS is a Doppler echocardiographic parameter used to evaluate pulmonary artery stiffness [10]. Although, right heart catheterization is the gold standard method for evaluating vascular stiffness and elasticity invasively, it is also possible to evaluate it with non-invasive methods such as TTE, CT and MRI due to the difficulty of clinical application [14,15]. TTE is preferred among non-invasive methods because of its easy accessibility, no need for radiation exposure and low cost. Several investigations have verified the clinical significance of PAS. Early detection of increased PAS evaluated in Behçet's disease patients by Yasar et al. [16], obstructive sleep apnea syndrome (OSAS) patients by Ozkececi et al. [17], asthma patients by Baysal et al [18], polycystic ovary syndrome patients by Abacioglu et al. [19], cirrhosis patients by Oz et al. [20], heart failure patients by Yenercag et al. [21], systemic lupus eritematosus (SLE) patients by Duman et al [22], and in human immunodeficiency virus-infected patients by Cerik et al. [23]. In

our study, PAS was found to be associated with right ventricular dysfunction. While a positive correlation was observed between increased sPAP and PAS, a negative correlation was detected between decreased PAS in patients with impaired RV-PA coupling. This finding was demonstrated for the first time in SSc patients without PH.

The RV-PA coupling describes the RV's adaptation to afterload. Progressive pulmonary vascular remodelling in PH causes an increase in pulmonary vascular resistance and pulmonary artery pressure, an extra strain on the contracting RV, and a change in RV-PA coupling [24]. TAPSE/sPAP ratio is a confirmed non-invasive assessment of RV-PA coupling that can be acquired simply during routine Doppler echocardiography. The TAPSE/sPAP ratio has been included to the list of additional echocardiographic indications suggestive of PH in the updated 2022 pulmonary hypertension (PH) recommendations. In a study by Colalilla et al., TAPSE/sPAP ratio < 0.55 mm/mmHg was a predictive risk factor for PH, and TAPSE/sPAP ratio \leq 0.32 mm/mmHg was found to be a high predictor for all-cause mortality [25]. In our study, significant deterioration was observed in echocardiographic parameters evaluating right ventricular functions, including PAS, in patients with impaired RV-PA coupling. A significant relationship was also detected between the increase in PAS and the impairment in RV-PA coupling.

Limitation

Our study has several limitations. First of all, our study was planned retrospectively, we do not have information about the clinical course of the patients, we do not have information about whether there is a response to PH treatments. Any quantitative method was used when evaluating the functional capacity of the patients. Our data on effort capacity was made by NYHA classification according to the answers given by the patients to questions about their daily activities. The 6-minute walk test could not be performed on the patients. If the gold standard method, RHC, was used instead of TTE, the diagnosis and follow-up of patients with PH would be more reliable. In addition, PH could be induced by exercise. It has been reported in the literature that the presence of PH can be investigated by exercise echocardiography in SSc patients and may contribute to the diagnosis [26]. In addition to this, it is a weakness that no studies using the more reliable speckle tracking echocardiography method, which can assess right ventricular systolic functions, have been done.

Conclusion

In our study, we observed higher PAS values in SScPH (-) patients compared to the control group and found a positive correlation between the increase in PAS and sPAP and a negative correlation between them and TAPSE/SPAP. In light of these findings, we recommend that PAS measurement, in addition to conventional methods, can be used in the early diagnosis of PH and evaluation of right ventricular dysfunction in the echocardiographic evaluation of SSc patients. Since, TTE can be used easily clinically, we think that a prospective controlled

study in larger populations is needed to evaluate its long-term clinical benefits.

Compliance with the Ethical Standards

Ethics Committee approval: The present study complies with the principles outlined in the Declaration of Helsinki. The study was approved by the Marmara University School of Medicine Research Ethics Committee. (approval number: 09.2017.613), and written informed consent was obtained from all participants.

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Conflict of interest: The authors have no potential conflicts of interest to disclose.

Authors contributions: Both authors contributed to the study conception and design. DA was the primary investigator of the study, DA: Design of the study, data collection, analysis of the data and drafting of the article, MD: Analysis and collecting of the data and drafting of the article. Both authors read and approved the final version of the article.

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