The occurrence of pulmonary hypertension in patients with systemic sclerosis hospitalized in The Department of Rheumatology and Internal Diseases Medical University of Białystok in years 2003-2004

Gińdzieńska-Sieśkiewicz E[1], Kowal-Bielecka O[1], Kita J[1], Lisowska A[2], Domysławska I[1], Musiał W[2], Sierakowski S[1]

[1] Department of Rheumatology and Internal Diseases, Medical University of Białystok, Poland
[2] Department of Cardiology, Medical University of Białystok, Poland

Abstract

Pulmonary hypertension (PH) is one the most fatal complications of systemic sclerosis (SSc). The aim of the present study was to investigate the occurrence of PH in SSc patients hospitalized in Department of Rheumatology and Internal Diseases University Hospital of Białystok in years 2003-2004. PH was defined as pulmonary artery systolic pressure (PASP) higher than 35 mmHg as evaluated by ECHO-Doppler.

We found PH in 23 out of 53 (43%) SSc patients included in the study. In the majority of patients 20/23 (87%) PH coexisted with the presence of scleroderma lung disease as evaluated by high resolution computed tomography of the lungs. In the remaining 3/23 (13%) patients isolated (arterial) PH was detected. Patients with isolated PH tend to have higher values of PASP (82±39.0 mmHg) than those with PH and interstitial lung disease (42.5±6.4 mmHg).

The results of our study indicate that PH is a frequent complication of SSc.

Key words: systemic sclerosis, pulmonary hypertension.

Introduction

Systemic sclerosis (SSc) is a systemic connective tissue disease of unknown etiology. It is characterized by immune disturbances, blood vessel and endothelium damage, as well as skin and internal organ fibrosis. The skin, the osteoarticular, cardiovascular, respiratory, and digestive systems as well as the kidneys and the nervous system are affected. The disease is chronic and progressive. The kind of the internal organ involvement decides of the course of the disease and the fate of the patient. So far, no drugs modifying the course of the disease have been found [1].

Clinically, there are diffuse systemic sclerosis (dSS) and limited systemic sclerosis (lSS) – earlier known as CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia) distinguished.

One of the most serious organ complications in the course of the SSc is the pulmonary hypertension (PH), which significantly increases mortality rate among the patients.

As far as pathogenesis is concerned, patients with the SSc reveal arterial PH, known also as isolated PH, which is characterized by obliterative changes of pulmonary arteries and forms of secondary PH. The latter may occur due to lung parenchyma damage in the course of the interstitial lung disease (lung fibrosis), left ventricular failure or thrombo-embolic changes [2,3].

Arterial PH usually concerns patients with limited SSc. It appears after a prolonged duration of the disease and is a result of the narrowing of pulmonary arteries. The appearance of the right heart failure (cor pulmonale) in patients with limited SSc correlates with nRNP antibody presence in serum. The rate of isolated PH occurrence is approximately 10-15% of patients [4,5,6].

Secondary pulmonary hypertension develops most frequently due to interstitial lung fibrosis and can occur in both diffuse and limited forms of the SSc. The former reveals interstitial pulmonary fibrosis and PH already in the early stage of the disease. PH is secondary to interstitial pulmonary fibrosis as a result of damage of lung tissues supporting blood vessels as well as the destruction of the vessels themselves. Hypoxia additionally strengthens hypertension due to reflex blood vessel contraction. According to various data, secondary pulmonary hypertension concerns more than 50% of patients with SSc [4,6].

Raynaud's pulmonary phenomenon is also taken into consideration in the pathogenesis of the pulmonary hypertension.

ADDRESS FOR CORRESPONDENCE:
Dr med. Ewa Gińdzieńska-Sieśkiewicz
Department of Rheumatology and Internal Diseases,
Medical University of Białystok
ul. M. Skłodowskiej-Curie 24a, 15-276 Białystok, Poland
Tel: +48 085 7468482; Fax: +48 085 7468606
e-mail: ewajsieskiewicz@op.pl

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Patients with the SSc often present ischemic heart disease and myocardial perfusion disorders that can contribute to the left-sided heart failure and subsequent increase in the pressure in the lung vasculature [3].

The aim of our study was to evaluate pulmonary hypertension occurrence rate in patients with SSc hospitalized in The Department of Rheumatology and Internal Diseases, Medical University of Białystok in years 2003-2004. Moreover, we attempted to determine clinical characteristics of patients with PH in the course of SSc.

Material and methods

The study was conducted in the group of 53 patients with diagnosed SSc, based on ARA classification criteria of 1980 [7], hospitalized in The Department of Rheumatology and Internal Diseases, University Hospital of Białystok in years 2003-2004. The clinical evaluation included sex, age, disease duration, disease subset, high resolution computed tomography (HRCT) of the lungs, pulmonary function tests and Doppler-echocardiography (ECHO). The patients were divided into 2 groups: those with the limited form of SSc and those with the diffuse one. All patients underwent serological examinations.

The indirect immunofluorescence test for antinuclear antibodies (ANA) and anticentromere antibodies (ACA) was performed and the presence of antibodies against topoisomerase I (anti-Scl-70) was evaluated with ELISA method. Patients' physical efficiency was assessed with the 6-minute-walk test. The pulmonary function tests (spirometry) were done in all patients. The presence of the interstitial lung disease was evaluated on the basis of HRCT of the lungs. Changes in lung tissue, visible in radiograms, were classified as without fibrotic features – the presence of so-called "ground glass" and as advanced fibrosis – the presence of so-called "honey combing" [8].

Pulmonary hypertension was evaluated using Doppler-echocardiography (ECHO). The examination was performed in a typical way, according to The American Society of Echocardiography instructions, with the apparatus Sonos 5500 using transthoracic transducer with a harmonic resolution 1.6-3.2 MHz. The systolic pressure in the pulmonary artery (pulmonary artery systolic pressure, PASP) was assessed based on the measurement of the maximum speed of the recoil wave of the tricuspid valve insufficiency. Then, the gradient of right ventricle/right atrium systolic pressure was calculated in the Bernoulli equation. The systolic pressure in the right ventricle, which is equal to the systolic pressure in the pulmonary artery (with lack of the pulmonary artery valvular stenosis), was calculated by adding the gradient value to the value of the right atrium pressure. The values above 35 mmHg of the PASP denoted the pulmonary hypertension (according to WHO) [9].

Statistical analysis

Statistical analysis was performed using the Mann-Whitney U test and the Fisher's exact test. P values less than 0.05 were considered statistically significant.

Table 1. **Clinical characteristics of the patients with systemic sclerosis**

Sex F/M no. (%)		51\2	(97/3)
Patients age (years) *		51 ± 14	
Disease duration (years)*		13 ± 10	
Disease subset	dSSc no. (%)	15	(28)
	lSSc no. (%)	38	(72)
PH(+)/PH (–) no. (%)		23/30	(43/57)
HRCT(+)/HRCT(–) no. (%)		35/18	(66/34)
ANA(+) no. (%)		53	(100)
Scl-70(+)/Scl-70(–) no. (%)		22/31	(41/59)
ACA(+)/ACA(–) no. (%)		8/45	(15/85)
HRCT(+) ground glass no. (%)		11	(20)
HRCT(+) honey combing no. (%)		24	(45)

* values are expressed as mean ±SD
HRCT(+)=high resolution computed tomography findings consistent with SLD; SLD=scleroderma lung disease; PH=pulmonary hypertension; ANA=antinuclear antibodies; anti-Scl-70=anti-topoisomerase I antibodies; ACA=anticentromere antibodies; lSSc – limited systemic sclerosis; dSSc – diffuse systemic sclerosis

Results

In the whole group of 53 patients with SSc, the PH was diagnosed in 23 (43%) patients while the remaining 30 (57%) patients did not present features of the PH.

Twenty out of 53 SSc patients revealed the PH coexisting with the interstitial pneumonia confirmed by the HRCT examination. The presence of the PH without coexisting interstitial pneumonia and hemodynamically significant left ventricle insufficiency was observed in 3/53 (6%) patients. Thus, the isolated PH was diagnosed in those patients.

Altogether, 35 out of 53 SSc patients had features of interstitial lung disease in the HRCT. In the whole group of SSc patients "ground glass" changes only were seen in the HRCT examination in 11 patients while the remaining 24 patients presented features of lung fibrosis.

HRCT revealed features of interstitial lung disease in 15/30 (50%) patients without the PH. The remaining 15/30 patients without PH had no changes in the HRCT.

Antinuclear antibodies (ANA) were found in all SSc patients and 22 (41%) patients had anti-topoisomerase I antibodies (anti-Scl-70). ACA were present in 8 (15%) patients, all with the diagnosed limited form of SSc. *Tab. 1* shows the general characteristics of 53 examined patients.

The mean duration of the disease in a group of 20 patients with PH and interstitial lung disease was 15±10 years with the mean age of the patients 55±12 years. Clinical evaluation of the physical efficiency based on the 6-min-walk test in that group of patients was mean 353±143 meters. The mean value of PASP in these subjects was 42.5±6.4 mmHg while their forced vital capacity (FVC) was 78.4±13.6% of predicted. Anti-Scl-70 antibody presence was observed in 11 out of 20 patients (55%) and ACA – only in 1 patient (5%).

Eleven patients out of 20 (55%) with the PH and interstitial

Table 2. **Comparison of of patients with and without PH**

	PH(+), HRCT(+)		PH(+), HRCT(–)		PH(–)	
Number of patients (%)	20	(37)	3	(6)	30	(57)
Age (years) *	55±12		53±11		49±15	
Disease duration (years) *	15±10		17±7		12±9	
6-min-walk test (meters) *	353±143		212±207		428±102	
PASP (mmHg) *	42.5±6.4		82.0±39.0		(N=3) 32.0±1.7	
FVC (% of predicted) *	78.4±13.6		92.0±15.6		92.0±15.8	
ANA no. (%)	20	(100)	3	(100)	30	(100)
Scl-70(+)/Scl-70(–) no. (%)	11/9	(55/45)	0	0	10/20	(33/67)
ACA(+)/ACA(–) no. (%)	1/19	(5/95)	1/2	(33/67)	5/25	(17/83)
Disease subset dSSc no. (%)	11	(55)	0	0	20	(67)
Disease subset lSSc no. (%)	9	(45)	3	(100)	10	(33)

* values are expressed as mean±SD; PH=pulmonary hypertension; PASP=pulmonary artery systolic pressure; FVC-forced vital capacity; HRCT – high resolution computed tomography; ANA=antinuclear antibodies; Scl-70=anti-topoisomerase I antibodies; ACA=anticentromere antibodies; lSSc – limited systemic sclerosis; dSSc – diffuse systemic sclerosis

Table 3. **Clinical characteristics of the patients with isolated PH**

	Patients with isolateded PAH						
	Age/years	**Disease duration**	**Disease subset**	**antibodies**	**PASP mmHg**	**6-min.-walk test**	**FVC (%)**
1	66	25	lSSc	ANA	110	110 m	84
2	47	16	lSSc	ACA	37	450 m	110
3	46	11	lSSc	ANA	99	75 m	82

PAH=pulmonary arterial hypertension; PASP=pulmonary artery systolic pressure; FVC=forced vital capacity; ANA=antinuclear antibodies; ACA=anticentromere antibodies; lSSc=limited systemic sclerosis; dSSc=diffuse systemic sclerosis

pneumonia had the diffuse form of SSc and the remaining 9/20 (45%) had the limited SSc (*Tab. 2*).

The PH without changes in the lung tissue (normal results of HRCT examination) was observed in 3 cases out of 53 subjects studied. In these 3 patients isolated PH (arterial PH) was diagnosed. Although the group was small its clinical differentiation was characteristic. The mean age was 53±11 years while the duration of the disease 17±7 years. The 6-minute-walk test was on average 212±207 meters. The mean value of PASP was 82±39 mmHg and FVC (Forced Vital Capacity) – 92±15.6%. Anti-Scl-70 antibodies were not found in any of these 3 patients and 1 person (33%) had positive ACA. The other 2 patients (67%) had ANA antibodies. All the patients suffered from the limited form of the SSc (*Tab. 2* and *3*).

The mean age of the patients without the PH was 49±15 years and the duration of the disease was 12±9 years. The mean test of the 6-minute-walk was 428±102 meters, and FVC was 92.0±15.8%. The majority of patients of this group did not reveal the tricuspid valve insufficiency, which prevented PASP measurement. Only 3 out of 30 patients presented a recoil wave of PASP values below 35 mmHg (mean 32±1.7 mmHg) through the tricuspid valve. Anti-Scl-70 antibodies were observed in 10 out of 30 patients (33%) while ACA – in 5/30 subjects (17%). The diffuse form of the SSc was diagnosed in 20 patients (67%) and the limited form – in 10 patients (33%) (*Tab. 2*).

The statistical analysis did not show any significant differences among the three groups of PH patients as far as the tolerance of physical effort is concerned (the 6-minute-walk test). However, low tolerance of physical effort of patients with isolated PH (p=0.07), as compared to those without the PH, should be noticed. It seems that lack of distinct statistical difference may occur due to small number of patients with the isolated PH.

FVC varied markedly between the groups of patients without the PH and those with the PH and interstitial lung disease (p=0.002), values statistically significant.

Discussion

As a result of our observation we can state that in the group of 53 patients with the SSc, most patients with the PH in the course of systemic sclerosis reveal the interstitial lung disease. It concerns both forms of the SSc: the limited and diffuse ones. In our study, the PH patients showed a predominance of Scl-70 antibodies.

The PH occurs frequently in patients with the SSc, even more than 50% of examined subjects can suffer from it. It is confirmed by the literature, where in the course of the diffuse SSc, the PH (as a result of the interstitial lung disease – secondary PH) occurs in up to 80% of patients [6,10,11]. The isolated (arterial) PH is observed mainly in the group of patients with the limited form of the SSc (approximately 10% of patients) as well as with the presence of ACA [5,6,12]. Our study presents similar results. The patients with the isolated PH constituted a small 3-person group (6%) with a differentiated clinical

course of the limited SSc. In this group the values of the PASP tend to be higher than in the group with the PH and interstitial lung disease. The physical efficiency of these patients was also lower than in the patients with PH and interstitial lung disease (the 6-min-walk test, mean 212±207 m as compared to mean 353±143 m). Other authors [5,12] also observed a similar clinical course.

It seems that the examined by us cases are the group of patients with the advanced form of the disease. Only few early stages of the PH are detected in the course of the SSc. It is probably due to early asymptomatic course of the PH, which afterwards gives symptoms of effort tolerance lowering and dyspnoea [4,6].

Pulmonary and cardiovascular complications appear most frequently in the first years of diffuse SSc. Therefore, patients should be under thorough control as far as organ complication occurrence is concerned [5,10]. The golden mean of diagnosis of PH is considered to be the right heart catheterization. However, it is an invasive examination and available only in highly specialized centers [3]. There were many studies performed which showed that ECHO examination with Doppler method is as much effective in evaluation of the PH as the catheterization. On the other hand, it is less accurate as there is lack of the recoil wave through the pulmonary arterial valve, which prevents a detailed evaluation but the ECHO examination provides additional information about the structure and function of the heart muscle [4,13,14]. The ECHO examination is nowadays considered as the screening of the PH in patients with the systemic sclerosis and as such should be conducted every year to enable introducing an early therapy of the PH [9,13].

The PH is an important diagnostic and therapeutic problem in patients with the SSc. In case of the limited SSc, a special attention should be paid to the presence of isolated arterial PH, which occurs usually after several years of the onset and can be characterized by a dramatic course due to high values of the pulmonary arterial pressure, deteriorating physical efficiency of the patients and lack of fully effective therapy. The PH secondary to the interstitial lung disease frequently occurs both in patients with diffuse and limited SSc [9]. Thus, it is necessary to perform early diagnostics to detect the PH (ECHO) in each patient who is suspected of suffering from an interstitial lung disease based on the spirometric examination [8]. It would allow to introduce early therapy of both lung fibrosis and PH in such patients.

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