How did the updated hemodynamic definitions affect the frequency of pulmonary hypertension in patients with systemic sclerosis?

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Abstract

Objective: Pulmonary hypertension (PH) is a one of the major causes of death in patients with systemic sclerosis (SSc). In this study, we investigated the impact of updated hemodynamic definition proposed by the 6th PH World Symposium (6th WSPH) on the frequency of PH and its subtypes in patients with SSc.

Methods: Patients with SSc admitted between 2015 and 2019 and who underwent right heart catheterization (RHC) were included. The frequency of PH and its subgroups based on the hemodynamic definitions of both 2015 European Society of Cardiology/European respiratory Society (ESC/ERS) PH guidelines and 6th WSPH was compared.

Results: Of the 65 patients with SSc, 23 (35.4%) had normal mean pulmonary arterial pressure (mPAP), 20 (30.8%) had mildly elevated mPAP (21–24 mm Hg), and 22 (33.8%) had PH [pulmonary arterial hypertension (PAH) (n=16, 24.6%), group 2 PH (n=5, 7.7%), group 3 PH (n=1, 1.5%)] according to the 2015 ESC/ERS PH definition. Based on the updated criteria, 7 (10.8% of total cohort) additional patients were reclassified as having PH [PAH (n=3), group 2 PH (n=3), group 3 PH (n=1)].

Conclusion: The impact of the updated definition on the frequency of PH and PAH in our cohort was greater than previously reported, which may be caused by the difference in screening strategies for PAH.

Keywords: systemic sclerosis, pulmonary hypertension, updated definition

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Introduction

Pulmonary hypertension (PH) is a serious complication and one of the major causes of mortality in patients with systemic sclerosis (SSc) (1). In the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines, PH is defined as an increase in the mean pulmonary arterial pressure (mPAP) ≥25 mm Hg measured by right heart catheterization (RHC) at rest (2). Pulmonary arterial hypertension (PAH) is a specific subtype of PH characterized by the presence of pre-capillary PH as pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg and increase in pulmonary vascular resistance (PVR) >3 Wood Units (WU) in the absence of other pre-capillary PH causes (2). According to the abovementioned hemodynamic definition, the estimated lifetime prevalence of PAH in SSc is between 8% and 14% (3).

Systematic analysis of RHC studies indicated that the normal range of mPAP in healthy individuals is 14±3 mm Hg, with an upper limit of 20 mm Hg (4). Based on this data, the Task Force of the 6th World Symposia on Pulmonary Hypertension (WSPH) proposed a new definition for all types of pre-capillary PH as mPAP >20 mm Hg, PCWP ≤15 mm Hg, and PVR ≥3 WU (5). Few data are available regarding the impact of the new definition on PH frequency in patients with SSc. In a recent study, Jaafar et al. (6) reported that 7 of 131 (5%) patients with no PH would be classified as PH after applying the updated criteria. However, different screening strategies for PH among centers may alter the impact

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of the new definition in patients with SSc. Thus, available data need to be validated in different cohorts.

In this study, we aimed to investigate the impact of updated hemodynamic definition on the frequency of PH subgroups in a single-center SSc cohort.

Methods

In this retrospective study, the medical records of patients with SSc admitted to the outpatient rheumatology unit between January 2015 and July 2019 were reviewed, and patients who underwent RHC were identified. All patients met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc (7). Demographic (age, sex), clinical (disease subtype, disease duration), and laboratory [autoantibody type, serum hemoglobin (Hb) level] data were obtained from the chart review. Results of pulmonary function test and transthoracic echocardiography nearest to RHC were also reviewed. Disease duration was defined as the period since the first non-Raynaud sign or symptom attributable to SSc. The presence of interstitial lung disease (ILD) was determined based on high-resolution computed tomography (HRCT) findings. The severity of ILD was assessed by combination of predicted force vital capacity (FVC) measurements and extent of parenchymal involvement in HRCT (8). Anemia was defined as serum Hb level <13 and <12 g/dL for men and women, respectively (9). The indications for RHC were 1) systolic pulmonary artery pressure (sPAP) ≥40 mm Hg on annual screening echocardiography in the absence of overt left-sided heart disease or significant lung fibrosis, or 2) clinical signs/symptoms attributable to PH that could not be explained by any other condition, even in the absence of elevated sPAP. Data collected from RHC reports included mPAP, PCWP, PVR, and cardiac index (CI). CI was measured using the thermodilution technique or estimated Fick method. The prevalence of PH and its subgroups based on the hemodynamic definitions of the 2015 ESC/ERS PH guideline and 6th WSPH was compared (Table 1).

This study was approved by the Institutional Ethics Committee.

Statistical analysis

Statistical analysis was performed using the SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as percentage. Continuous variables were expressed as mean [standard deviation (SD)] or median [interquartile range (IQR)] for normally distributed data and skewed data, respectively. Normality of data was assessed using the Kolmogorov–Smirnov test. Chi-squared and Fisher exact tests were used to compare categorical variables. Student t test, Mann–Whitney U test, one-way analysis of variance, and Kruskal–Wallis H test were used to compare continuous variables between independent groups. A significance level of 0.05 was used for all statistical tests.

Results

Among 293 (91.2% female) patients with SSc, 77 (26.2%) were evaluated with RHC. Twelve patients were excluded due to missing hemodynamic data for PVR, PCWP, or both (8 for PVR, 4 for both). The mPAP category of excluded patients were ≤20 mm Hg in 3, 21–24 mm Hg in 4, and ≥25 mm Hg in 5 patients. Of the five

Table 1. Hemodynamic definitions of pulmonary hypertension

	2015 ESC/ERS	6th WSPH
Group 1 PH (PAH)*	mPAP≥25 mm Hg PCWP≤15 mm Hg PVR >3 WU	mPAP>20 mm Hg and PVR≥3 WU PCWP≤15 mm Hg
Group 2 (post-capillary) PH (left-sided heart disease)	mPAP≥25 mm Hg PCWP>15 mm Hg • Isolated post-capillary PH DPG<7mm Hg and/or PVR≤3WU • Combined post-capillary and pre-capillary PH DPG≥7 mm Hg and/or PVR>3 WU	mPAP>20 mm Hg PCWP>15 mm Hg • Isolated post-capillary PH PVR<3 WU • Combined post-capillary and pre-capillary PH PVR>3 WU
Group 3 PH (lung diseases and/or hypoxia)**	mPAP≥25 mm Hg PCWP≤15 mm Hg	mPAP>20 mm Hg and PVR≥3WU PCWP≤15 mm Hg

*In the absence of all other PH causes.
**Consider lung disease by symptoms, signs, risk factors, pulmonary function tests, diffusion capacity for carbon monoxide, chest radiography/HRCT, arterial blood gas analysis.
ESC/ERS - European Society of Cardiology/European Respiratory Society; WSPH - World Symposia on Pulmonary Hypertension; PH - pulmonary hypertension; PAH - pulmonary arterial hypertension; mPAP - mean pulmonary arterial pressure; PVR - pulmonary vascular resistance; WU - Woods unit; PCWP - pulmonary capillary wedge pressure; DPG - diastolic pressure gradient; HRCT – high resolution computed tomography; FVC - force vital capacity

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patients with mPAP ≥25 mm Hg, the final diagnosis was group 2 and 3 PH in 1 and 4 patients, respectively (3 patients had FVC <70%, and 1 patient had extensive ILD on HRCT). PAH-specific therapy had been started in 3 of 4 patients with group 3 PH in external centers.

The final study group consisted of 65 (93.8% female) patients. The mean age and disease duration were 55.8 years (11.6 years) and 10.3 years (7.6 years), respectively. Diffuse disease and ILD were found in 11 (16.9%) and 42 (64.6%) patients, respectively.

Based on the 2015 ESC/ERS hemodynamic definitions, 22 (33.8%), 20 (30.8%), and 23 (35.4%) patients had PH (≥25 mm Hg), mildly elevated mPAP (21–24 mm Hg), and normal mPAP (≤20 mm Hg), respectively. Table 2 shows the patient characteristics. The final diagnosis of the patients with PH after multidisciplinary evaluation were PAH in 16 (24.6%), group 2 PH in 5 (7.7%) and group 3 PH in 1 (1.5%) patient. Patients with PH were significantly older than those with mPAP ≤20 mm Hg (p=0.030). Echocardiographic sPAP in patients with PH was higher than that in other groups; however, it was similar between patients with mPAP 21–24 mm Hg and mPAP ≤20 mm Hg (Table 2). Echocardiographic sPAP was <40 mm Hg in 3 (13.6%) patients with PH, 5 (25.0%) patients with mPAP 21–24 mm Hg, and 4 (17.4%) patients with mPAP ≤20 mm Hg.

Based on the updated classification, 21 (32.3%) patients met the new definition of pre-capillary PH. Of these 19 (29.2%) patients had PAH and 2 (3.1%) patients had group 3 PH. 8 (12.3%) patients were classified as having post-capillary PH (mPAP >20 mmHg and PCWP >15 mmHg).

Figure 1 shows the reclassification of 20 patients with mPAP 21–24 mm Hg PH based on the 6th WSPH definition. Seven (35%) of these patients were classified as having PH [PAH (n=3), group 2 PH (n=3), group 3 PH (n=1)]. The PVR values of 3 patients who were reclassified as PAH were 5.3, 4, and 3 WU, respectively. Because the PVR values were <3 WU, 13 patients with mPAP >20 mm Hg and PCWP ≤15 mm Hg did not meet the criteria for pre-capillary PH. Among these unclassified patients, the mean serum Hb level in patients with PVR between 2 and 3 WU was slightly lower than that in those with PVR <2 WU (12.4 vs. 13.2 g/dL, p=0.337). The frequency of anemia was also higher in patients with PVR between 2 and 3 WU (50% vs. 20%, p=0.565), but it was not significantly different. No difference was observed in the mean CI between patients with PVR between 2 and 3 WU and those with PVR <2 WU (3.0±0.8 vs. 3.6±0.6, p=0.088) (data for CI and serum Hb were available for 12 patients in the unclassified group).

In a median (IQR) follow-up time of 2.8 (1.1–5.2) years, 5 of the 20 patients with mPAP 21–24 mm Hg had subsequent RHCs.

Table 2. Baseline characteristics of patients

	Normal (mPAP ≤20 mm Hg) (n=23)	Mildly elevated mPAP (mPAP 21–24 mm Hg) (n=20)	PH (mPAP ≥25 mm Hg) (n=22)	*P*
Age, years	51.8 (12.0)	56.3 (10.2)	59.6 (11.4)	0.074
Female	23 (100.0)	17 (85.0)	21 (95.5)	0.116
Disease duration, years	11.2 (8.4)	11.3 (7.0)	8.4 (7.3)	0.390
Diffuse disease	5 (21.7)	3 (15.0)	3 (13.6)	0.740
Interstitial lung disease	13 (56.5)	16 (80.0)	13 (59.1)	0.221
FVC, predicted%, median (IQR)	90 (77-106)	80 (75-88)	78 (64-91)	0.193
Autoantibodies				
Anti-SCL-70	10 (43.5)	14 (70.0)	10 (47.6)	0.182
Anti-centromere	4 (17.4)	2 (10.0)	8 (38.1)	0.076
Echocardiographic sPAP, mm Hg, median (IQR)	40 (40-45)	45 (36-53)	57.5 (45-80)	**0.003**[1]
Hemoglobin, g/dL*	11.5 (1.4)	12.7 (1.3)	12.5 (1.2)	**0.013**[2]
RHC findings				
mPAP, mm Hg, median (IQR)	18 (17-19)	23 (21-24)	35.5 (28-45)	**<0.001**[3]
PCWP, mm Hg, median (IQR)	10 (8-10)	10.5 (10-13)	13 (10-15)	**0.002**[4]
PVR, WU, median (IQR)	1.8 (1.3-2.1)	2.0 (1.7-2.9)	5.1 (4.1-6.7)	**<0.001**[5]
CI, L/min/m²*	2.6 (0.6)**	3.0 (0.8)	2.6 (0.7)	0.192

Values are n (%) and mean (standard deviation) unless otherwise indicated. *Data for CI and Hb were available for 61 and 62 patients, respectively. **Two patients had myocardial involvement (one had restrictive cardiomyopathy and the other had right ventricular cardiomyopathy), and one patient had multivessel coronary artery disease.
[1] *P*1=0.378, *P*2=0.001, *P*3=0.022
[2] *P*1=0.012, *P*2=0.018, *P*3=0.776
[3] *P*1=<0.001, *P*2=<0.001, *P*3=<0.001
[4] *P*1=0.034, *P*2=0.001, *P*3=0.099
[5] *P*1=0.150, *P*2=<0.001, *P*3=<0.001
*P*1=normal vs. mildly elevated mPAP, *P*2=normal vs. PH, *P*3=mildly elevated mPAP vs. PH.
mPAP - mean pulmonary arterial pressure; PH - pulmonary hypertension; FVC - force vital capacity; IQR - interquartile range; sPAP - systolic pulmonary arterial pressure; RHC - right heart catheterization; PCWP -pulmonary capillary wedge pressure; PVR - pulmonary vascular resistance; WU - Woods unit; CI - cardiac index

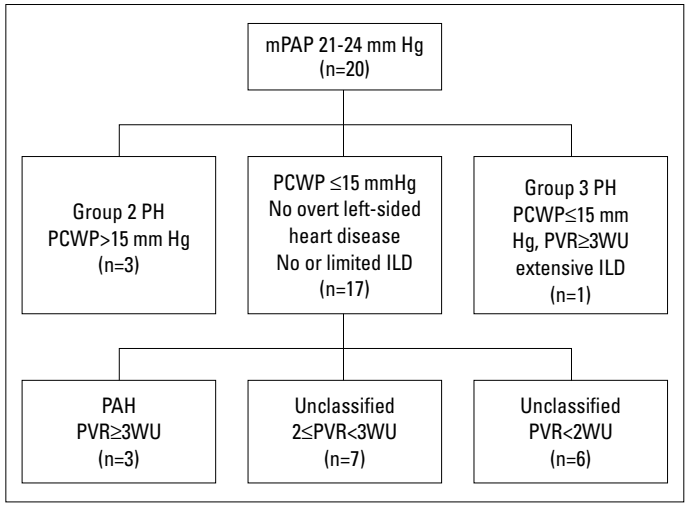

Figure 1. Reclassification of patients with mildly elevated PH (mPAP 21–24 mm Hg) based on the updated definition

One patient was diagnosed with PAH 1.8 years after the first RHC (mPAP=34 mm Hg). Group 2 PH was found in another patient (mPAP=28 mm Hg, PCWP=18 mm Hg) at the third RHC 1.9 years after the first RHC. Two patients had mPAP 21–24 mm Hg again on subsequent RHCs performed 0.9 and 1.4 years after the first RHC, respectively. In the last patient, mPAP was normal 6 years after the first RHC. Subsequent RHC was not needed in 15 patients due to stable clinical findings, 6-min walk distance, serum brain natriuretic peptide level, and echocardiographic sPAP.

Discussion

The study results suggest that the updated hemodynamic definition has a greater impact on the frequency of PH and its subgroups than previously published data. In total cohort, the frequency of PAH, group 2 and 3 PH increased by 4.6%, 4.6%, and 1.6%, respectively. Based on the new definition, 3 (15%) of the 20 patients with mildly elevated mPAP (21–24 mm Hg) were reclassified as PAH.

Data about the impact of updated definition proposed by the 6th WSPH on reclassification in patients with SSc are limited. Jaafar et al. (6) applied the new criteria to their SSc cohort including 268 patients and reported a 1.5% (from 33.2% to 34.7%) and 0.3% (from 20.9% to 21.2%) increase in the frequency of PH and PAH, respectively. Only 1 (0.5%) of 50 patients with mPAP 21–24 mm Hg was reclassified as PAH. Another study that also excluded patients with overt left heart disease or significant pulmonary fibrosis reported a 1.4% increase in the frequency of PAH. In that study, 8% of patients with mPAP 21–24 mm Hg were reclassified as PAH (4 in 55) (10). The most striking difference of our cohort from other studies is that patients with mPAP 21–24 mm Hg account for approximately one-third of the whole cohort. However, this frequency was 18.6% and 19% in other cohorts (6, 10). Different PAH screening algorithms among centers might have led to this discrepancy. We mainly used annual echocardiographic evaluation for PAH screening, whereas the DETECT algorithm was the preferred method in other studies. Briefly, the DETECT algorithm is an evidence-based tool that identifies patients with SSc with PAH, which combines several variables in a two-step decision tree (11). The DETECT algorithm includes pulmonary function tests [diffusing capacity for carbon monoxide (DLCO) <60%] as an entry criterion; however, we did not use DLCO in PAH screening.

Analysis of the hemodynamic data of the DETECT study showed that mildly elevated PH (mPAP 21–24 mm Hg) is an intermediate stage between normal mPAP and PAH (12). Compared with those with normal mPAP, patients with SSc with mPAP 21–24 mm Hg have impaired exercise capacity, as shown by the 6-min walk test and cardiopulmonary exercise test (13). Moreover, those patients are at increased risk for developing PAH (14-16). Coghlan et al. (14) showed that 33% of patients with SSc with mPAP 21–24 mm Hg developed resting PH in a median follow-up of 3 years. In another UK cohort, 18.5% and 27.1% of patients with mPAP 21–24 mm Hg converted to PAH within 3 and 5 years, respectively (15). In our study, 2 of the 5 patients with mPAP 21–24 mm Hg and subsequent RHCs developed PH during follow-up. One of them developed PAH, whereas the other patient was diagnosed with group 2 PH. Although the numbers are low, our results were consistent with the previous literature.

The 6th WSPH Task Force arbitrarily recommended a PVR cut-off of 3 WU for the diagnosis of all types of pre-capillary PH to discriminate the mPAP elevation driven by other causes than pulmonary vasculopathy (e.g., increased cardiac output and/or PCWP). A systematic review by Kovacs et al. (4) indicated that the upper limit of PVR in healthy subjects from all age categories is <1.5 WU. Addition of 2 SD to this upper limit leads to a PVR threshold of 2 WU. Although it is yet unclear whether patients with SSc with mildly elevated PH and PVR ≥2 WU are at particular risk for further progression of pulmonary vasculopathy, a recent study demonstrated that patients with SSc with mPAP 21–24 mm Hg and PVR ≥2 WU (without significant lung or left-sided heart disease) had markedly impaired right ventricular functions and reduced survival compared with those with PVR <2 WU (9). Based on these results, authors concluded that a PVR cut-off value of 3 WU for the diagnosis of pre-capillary PH is too conservative, and a cut-off value of 2 WU may allow early detection of clinically significant pulmonary vasculopathy. Decreasing the PVR cut-off from 3 to 2 WU resulted in seven-fold increase in the incidence of newly diagnosed PAH (from 1.4% to 9.8%) (9). Similar to the abovementioned study, the use of 2 WU threshold would lead to a substantial increase in the frequency of newly diagnosed PAH from 4.6% to 15.3% in our cohort. By contrast, modest elevations in PVR do not always necessarily reflect the presence of severe pulmonary vasculopathy. For instance, in the course of chronic hemolytic anemias, a clinical condition resembling PAH with modest elevation in PVR may

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occur (17). In patients with anemia, hyperdynamic pulmonary circulation with increased mPAP and decreased PVR is typical. Patients with SSc are at particular risk for anemia due to several reasons (18, 19). In our study, patients with PVR between 2 and 3 WU more frequently had anemia and lower mean serum Hb levels than those with PVR below 2 WU. By contrast, no striking difference was found between the CI values of these two groups. Defective vasodilatation is characteristic of vasculopathy in SSc, which may involve any organ system, including the pulmonary vascular bed (20-22). Although a proper statistical comparison could not be performed because of the small number of patients, one can speculate that mild anemia may lead to a mild increase in PVR in patients with defective vasodilatation, such as SSc. However, this hypothesis needs to be confirmed in further research.

Our study showed that the number of cases with both PH and PAH significantly increased by using the new definition of PH. This change will allow early treatment of high-risk patients with PAH with SSc. However, data about the treatment strategy of this patient group are limited. The differential diagnosis is challenging in these patients with mildly elevated pulmonary pressures, and using PAH-specific agents has a potential to aggravate underlying left-sided heart disease (23). Therefore, these patients should be closely followed up until more data are available. More data are also needed regarding the follow-up strategy of patients with unclassifiable PH (mPAP>20, PCWP≤15 mm Hg, and PVR <3 WU).

The main limitation of our study is its retrospective design and the limited number of patients with SSc. In addition, comparison of our results with previous studies is difficult because the screening strategies for PAH and indications for RHC are different.

Conclusion

In conclusion, the impact of updated hemodynamic definition on the frequency of PAH in our cohort was greater than the previous studies, probably due to overrepresentation of patients with mPAP 21–24 mm Hg. The difference in screening strategies for PAH might have also led to this finding. Prospective long-term studies are needed to examine follow-up strategies for patients with mildly elevated mPAP and those who remain unclassified.

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