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ORIGINAL ARTICLE

Pulmonary hypertension in Spanish patients with systemic sclerosis. Data from the RESCLE registry

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Abstract

Introduction Our objective was to evaluate the pulmonary hypertension (PH) data for Spanish patients with systemic sclerosis (SSc), define the PH types and determine the associated factors.

Method Descriptive study of PH-related data from the multicentre RESCLE registry. Estimated systolic pulmonary artery pressure (esPAP), measured via echocardiogram was considered elevated if ≥ 35 mmHg. Left heart disease (LHD) and interstitial lung disease (ILD) were identified. When performed, data from right heart catheterisation (RHC) were collected.

Results esPAP was elevated in 350 of 808 patients (43.3%). One hundred and forty-four patients (17.8%) were considered to have PH (88 via RHC and the rest due to elevated esPAP along with evidence of significant LHD or ILD): PAH 3.7%, secondary to ILD 8.3%, secondary to LHD 2.8% and unclassified 3%. Prevalence of elevated esPAP was greater in diffuse SSc (dSSc) than in limited scleroderma (lSSc) (50.5 vs. 42.2%, p 0.046). In the group with elevated esPAP, a lower prevalence of anti-centromere antibodies (41.9% vs. 52.3%, p 0.006) and a greater prevalence of anti-topoisomerase-1 antibodies (ATA) (25.1% vs. 18.6%, p 0.04) were observed compared to the group with normal esPAP. Patients with elevated esPAP had a lower rate of digital ulcers (50.6% vs. 60.2%, p 0.007) and esophageal involvement (83.6% vs. 88.7%, p 0.07) and higher rate of renal crisis (4.6% vs. 1.8%, p 0.066).

Conclusions Prevalence of PAH was lower than expected (3.7%). Probability of having elevated esPAP was higher among patients with dSSc and among those with ATA.

Keywords Anti-centromere antibodies · Pulmonary hypertension · Systemic sclerosis

Introduction and objective

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg measured via right heart catheterisation (RHC) at rest. The different processes with which it is associated are classified in groups that share pathogenic and haemodynamic characteristics, conditioning treatment differences [1]. Pulmonary arterial hypertension (PAH) is a variant of PH caused by an obstructive proliferation of pulmonary arterioles. It may be idiopathic or associated with various processes. These include connective tissue diseases, especially systemic sclerosis (SSc). Patients with SSc constitute a population at risk of suffering PAH, which is a serious and relatively frequent complication. SSc-associated PAH (SSC-PAH) has worse evolution and response to treatment than those observed in idiopathic PAH (IPAH) [2–4]. For all of these reasons, clinical practice guidelines recommend an annual screening for PAH via an echocardiogram to ease early detection and treatment, aiming to improve its prognosis [1, 5]. Suspected PH in SSc patients requires a careful differential

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diagnosis to distinguish PAH from PH secondary to left heart disease (LHD), interstitial lung disease (ILD) and chronic thromboembolic disease (especially in patients with antiphospholipid antibodies) since their treatments are different. This differentiation may be very difficult in SSc, in light of the possible coexistence of pulmonary vasculopathy with different degrees of ILD and LHD.

In Spain, only one single-centre study has been published to date evaluating the frequency of PAH and other forms of PH in patients with SSc [6]. The RESCLE registry gathers an extensive and multicentre series of Spanish patients with SSc. Our objective was to evaluate the PH data among patients included in the registry, define their HP types and determine which factors are associated with PAH.

Patients and methods

Descriptive transversal study of PH-related data collected in the multicentre RESCLE registry. The RESCLE registry was created by the Spanish Internal Medicine Society in 2006 with the aim of compiling a large series of Spanish SSc patients. Thirty Spanish hospitals are participating in the patient recruitment, with the approval of their respective ethics committees. Epidemiological, clinical, laboratory and immunological data are collected according to a standard protocol. A diagnosis of SSc is considered when the patients met the ACR/EULAR 2013 criteria [7] and/or the modified classification criteria proposed by LeRoy and Medsger [8]. Thus, four groups of patients with SSc were established according to the extension of their cutaneous sclerosis [8]:

1. Pre-SSc, defined by the presence of Raynaud's phenomenon (RP), characteristic SSc nailfold capillaroscopic changes and/or disease-specific autoantibodies but no skin thickening.
2. Limited SSc (lSSc), when skin thickening was confined distally to the elbows and knees or the face.
3. Diffuse SSc (dSSc), when skin thickening extended proximally to the elbows and knees or included the trunk.
4. Sine scleroderma SSc (ssSSc), defined by the presence of RP, scleroderma clinical features, and disease-specific autoantibodies but no cutaneous sclerosis.

The visceral involvement data, capillaroscopy patterns and immunological changes were considered in the same way in which they were defined in prior works by RESCLE Group [9].

Via an echocardiogram, the estimated systolic pulmonary artery pressure (esPAP) was calculated and left ventricular systolic or diastolic dysfunction data were identified. In order to establish an adequate cutoff point, and consistent with previous studies [5, 10], the esPASP was deemed elevated if ≥ 35 mmHg. Left ventricular systolic dysfunction was defined as an ejection fraction ≤ 45%. The existence of left ventricular diastolic dysfunction was estimated using the measurement of the ratio between the early maximal ventricular filling velocity and the late filling velocity (E/A ratio). From the respiratory perspective, the existence of radiological alterations (via chest X-ray and/or computed tomography [CT]) and alterations in the functional tests (forced vital capacity [FVC] and the forced expiratory volume in the first second [FEV1]) were considered.

The definitions of PH (precapillary, postcapillary and PAH) and their classification followed international consensus [1]. PH was defined as an mPAP ≥ 25 mmHg measured via RHC at rest. Precapillary PH was characterised by a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and postcapillary PH by a PCWP > 15 mmHg. Precapillary PH was considered to be secondary to an ILD if the FVC was < 60% of the theoretical value, and the extent of radiological alterations exceeded 20%. The term PAH refers to a group of patients with precapillary PH with pulmonary vascular resistance > 3 WU in the absence of other causes of precapillary PH (such as pulmonary diseases or pulmonary thromboembolism). Patients with an mPAP between 21 and 24 mmHg were considered to have borderline PAH.

Statistical analysis The mean and standard deviation of the continuous quantitative variables were determined. The chi-square test (or Fisher's exact test when necessary) was used for qualitative variables, and Student's *t* test for quantitative variables. All analyses were performed using the SPSS 15.0 software for windows (SPSS, Chicago, IL). Statistical significance was set at $p < 0.05$.

Results

A total of 1463 patients included in the registry were collected (1302 women, 89%): 860 with lSSc (58.8%), 348 with dSSc (23.8%), 142 with ssSSc (9.7%), 97 with pre-SSc (6.6%) and 16 cases in which the subtype was not available (1.1%). Their mean (standard deviation (SD)) age at diagnosis was 51.8 ± 15.4 years, and the mean time of evolution from diagnosis to their inclusion in the registry was 8.2 ± 7.7 years.

At least one echocardiogram had been performed in 1307 patients (89.3%), and the esPAP value was available in 808 (55.2%), of which 350 had an esPAP ≥ 35 mmHg (43.3%). The mean time of evolution from diagnosis was similar for patients with esPASP within normal ranges or elevated (9.2 ± 7.3 and 9.3 ± 8.1 years, *p* 0.758).

A RHC was performed in 114 patients with esPAP ≥ 35 mmHg with the following result: PH confirmed in 79, absence of PH in 14 and borderline PH in 9; the mPAP value was not present in the other 12 patients (6 with echocardiographic data of left ventricular diastolic dysfunction and 2

with ILD with FVC ≤ 60%). The RHC was also performed in 20 patients with esPAP < 35 mmHg, detecting PH in 9 and borderline PH in 2.

Of the 88 patients with PH confirmed via RHC (10.9% of patients with available esPAP values), 36 had a precapillary PH pattern (26 with ILD, 6 of them with FVC ≤ 60%) and 16 had a postcapillary PH pattern; the PH pattern could not be classified in 36 cases due to the unavailability of the PCWP value (27 with ILD, 12 of them with FVC ≤ 60%, and 10 with echocardiographic evidence of left ventricular diastolic dysfunction, one of them also with systolic dysfunction). Of the 236 patients with esPAP ≥ 35 mmHg not tested with RHC, 7 had echocardiograph data of left ventricular systolic dysfunction and 47 had ILD with FVC ≤ 60%. In total, 144/808 (17.8%) patients with known esPAP were considered to have PH: 30 with PAH (3.7%), 67 with PH secondary to ILD (8.3%), 23 with PH secondary to LHD (2.8%) and 24 with unclassified PH (3%). These data are summarised in Figs. 1 and 2 and in Table 1.

The prevalence of elevated esPAP differed significantly between the different SSc subtypes. An esPAP ≥ 35 mmHg was found in 205/486 patients with lSSc (42.2%), 105/208 with dSSc (50.5%), 34/78 with ssSSc (43.8%) and 4/34 with pre-SSc (11.8%). The prevalence of esPAP ≥ 35 mmHg was significantly lower in patients with pre-SSc compared to the rest of SSc subtypes ($p < 0.001$) and was significantly higher in patients with dSSc compared to lSSc (p 0.046). These data are summarised in Table 2.

Among the 808 patients with known esPAP values, the positivity or negativity of anti-centromere antibodies (ACA) was registered for 739 (91.5%) and that of anti-topoisomerase-1 antibodies (ATA) in 760 (94%). ACA were positive in 131/313 patients with esPAP ≥ 35 mmHg (41.9%) compared to 223/426 with normal esPAP (52.3%). ATA were positive in 83/331 patients with esPAP ≥ 35 mmHg (25.1%) compared to 80/429 with normal esPAP (18.6%). The prevalence of ACA was significantly lower (41.9% vs. 52.3%, p 0.006), and the prevalence of ATA was significantly higher (25.1% vs. 18.6%, p 0.04) in patients with esPAP ≥ 35 mmHg than in patients with esPAP < 35 mmHg. These data are summarised in Table 3.

Among the characteristic symptoms of SSc, patients with esPAP ≥ 35 mmHg developed digital ulcers with a significantly lower frequency than those with esPAP < 35 mmHg (50.6% compared to 60.2%, p 0.007). A higher rate of renal crisis (4.6% compared to 1.8%, p 0.066) and lower rate of esophageal involvement (83.6% compared to 88.7%, p 0.07) were also observed in patients with esPAP ≥ 35 mmHg. In both cases, the difference was close to statistical significance. The prevalence of RP, liver disease and thyroid function alterations did not differ between groups.

Discussion

Among the wide series of patients collected in the RESCLE registry, after global analysis of the available data, 144 patients were determined to have PH (17.9% of evaluable patients), confirmed via RHC in 88 (10.9%). PAH was diagnosed in 3.7% (all confirmed with RHC), PH secondary to LHD in 2.8%, PH secondary to ILD in 8.3% and unclassified PH in 3% (all confirmed with RHC). Elevated esPAP was significantly more prevalent in patients with dSSc than with lSSc, and in patients with ATA than with ACA. Patients with elevated esPAP had greater frequency of renal crisis, and lesser frequency of digital ulcers and esophageal involvement.

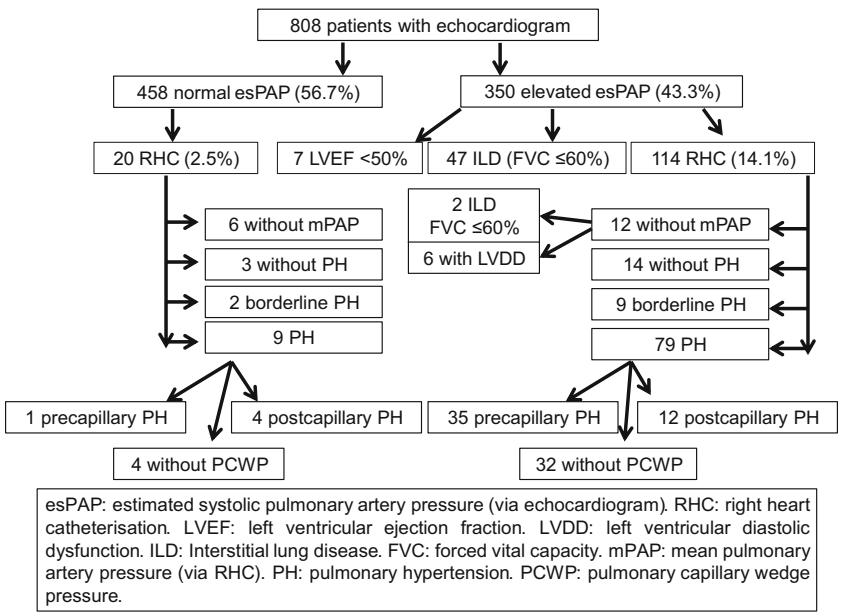

Fig. 1 Result of the screening and diagnosis process of pulmonary hypertension

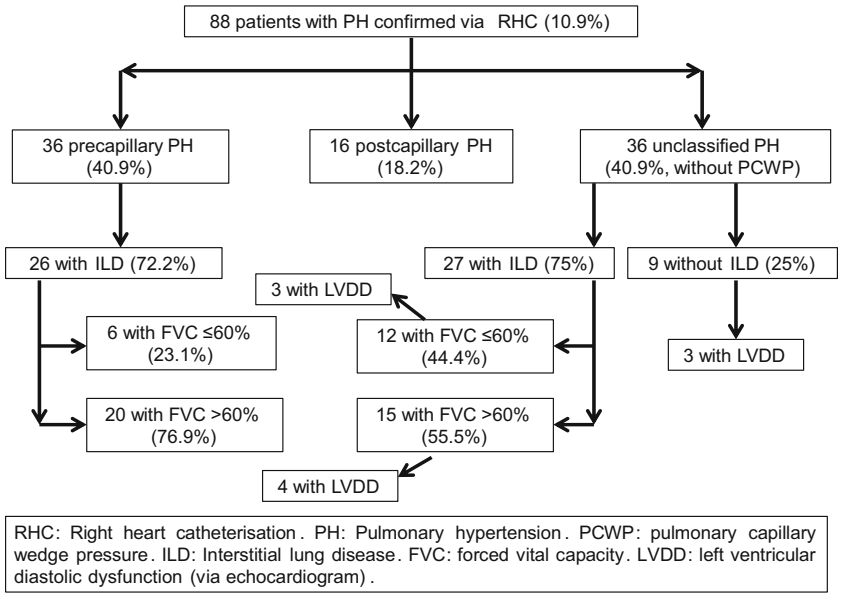

Fig. 2 Classification of patients with pulmonary hypertension diagnosed via right heart catheterisation

PAH had an important negative impact on prognosis for SSc patients. Pulmonary involvement, both due to pulmonary fibrosis and to PAH, is the primary cause of death in the majority of published series [11–15]. In the RESCLE registry [9], pulmonary involvement was the primary cause of death; 25.4% of patients died from ILD and 16.6% from PAH, which was the primary cause of death in patients with lSSc.

The frequency of PAH in patients with SSc varies widely between publications, mainly due to the definitions used. Pope et al. [16] (33%), Wigley et al. [17] (26.7%) and MacGregor et al. [18] (13%) based their definitions solely on echocardiograpic data. Mukerjee et al. [19] and Vonk et al. [20] described a similar rate of precapillary PH (12% and 10%, respectively), but they did not distinguish between its different causes. Hachulla et al. [12] found a frequency of 8%, but excluded patients with ILD from the study. Avouac et al. [21] rigorously quantified the different PH varieties in a wide series. They verified the existence of precapillary PH in 5% of patients (PAH in 3.6% and secondary to ILD in 1.9%) and postcapillary PH (secondary to LHD) in 1.4%. The data reported from an Italian cohort were similar [22]. In the DETECT study, conducted in a population with SSc and a high risk of PAH, the frequency was 19%, compared to 6% both for PH secondary to ILD and for postcapillary PH [23]. Our previous study found numbers between those from DETECT and those of Avouac et al.: PAH in 13.6%, postcapillary in 3.8%, secondary to ILD in 2.2% and chronic thromboembolism in 1.1%[6]. These data are similar to those from a multicentre Australian cohort (PAH in 11.8%) [24]. In our study, the prevalence of confirmed PAH was 3.7% with a higher frequency of PH secondary to ILD (8.3%) and lower frequency of PH secondary to LHD (2.8%). However, a 3% of patients with PH confirmed via RHC could not be classified, which could lead to an underestimate of the frequency of PAH. Table 4 summarises the frequency of each type of PH found in the most important series, compared to ours.

SSc patients constitute a group at risk of developing PAH and, therefore, are subject to early diagnosis and treatment [1, 5, 6, 25]. The associated poor prognosis emphasises the importance of early detection. In the EARLY study [26], starting bosentan treatment in a cohort of patients with early-stage PAH (17% had SSc) determined an improvement in prognosis. Humbert et al. [27] confirmed that applying an early PAH

Table 1 Prevalence of pulmonary hypertension and its categories

Pulmonary hypertension (PH)	144/808 (17.8%)
PH due to interstitial lung disease	67 (8.3%)
Pulmonary arterial hypertension	30 (3.7%)
PH due to left heart disease	23 (2.8%)
Unclassified PH	24 (3%)
Borderline PH[a]	11/808 (1.4%)

[a] Patients with borderline PH were not included among 144 patients with PH

Table 2 Prevalence of the systemic sclerosis subtypes in patients with elevated estimated systolic pulmonary artery pressure via echocardiogram

Systemic sclerosis subtypes	Patients	%	*p*
Limited	205/486	42.2	
Diffuse	105/208	50.5	0.046[♯]
Sine scleroderma	34/78	43.6	
Pre-scleroderma	4/34	11.8	< 0.001[*]

[♯] Significant difference from the group with limited scleroderma

[*] Significant difference from the rest of groups

Table 3 Prevalence of the autoantibodies subtypes in patients with elevated esPAP via echocardiogram

Antibody subtype	esPAP	Patients	%	*p*
Anti-centromere (ACA) + (354/739 patients evaluated)	Elevated	131/313	41.9	0.006
	Normal	223/426	52.3	
Anti-topoisomerase-1 (ATA) + (163/760 patients evaluated)	Elevated	83/331	25.1	0.04
	Normal	80/429	18.6	

detection programme in SSc patients allows for detection and treatment in earlier phases, with a favourable impact on survival. However, and despite the clearly established recommendation in international consensus, screening programs are not entrenched in usual clinical practice, as Morrisroe et al. confirmed among Australian rheumatologists [24]. In our study, 89.3% of the patients included in the registry had at least one echocardiogram done during their evolution, although the esPAP value was not present in a significant percentage of them (38.2%). It must be considered that tricuspid failure is not detected in a significant proportion of echocardiograms, and therefore, the esPAP cannot be calculated. The number of RHCs conducted was low (114/350 patients with elevated esPAP, 32.57%), and the absence of the PCWP value impeded classifying the PH in 36 cases (40.9% of patients with PH confirmed via RHC). Nevertheless, it seems that clinicians are reluctant to perform haemodynamic tests in their usual practice. Morrisroe et al. [24] confirmed that the number of RHCs carried out in patients considered at moderate or high risk of PAH was low (29.7%), citing reasons such as conserved functional capacity or attribution to an underlying mild ILD.

Generally, it is accepted that PAH is more common in patients with lSSc than those with dSSc, and in patients with ACA than those with ATA [24, 28–30]. However, Denton et al. found that PAH is almost as common in patients with dSSc as in lSSc [31]. Hesselstrand et al. [32] found a significantly higher risk of having an elevated transtricupsid gradient in the echocardiogram in patients with ATA and found no association with ACA or SSc subtype. This association was also not found in a previous Spanish study [6]. In the German registry, PAH was more common in patients with dSSc than lSSc [33]. Aligned with these findings, the prevalence of elevated esPAP in the RESCLE series was significantly higher in patients with dSSc compared with lSSc, and in patients with ATA compared with ACA.

A significantly higher frequency of some clinical symptoms was described in patients with SSc and PAH than in those without. A review by Denton et al. [31] found that clinical factors associated with developing PAH were the degree of cutaneous thickening, more severe peripheral vasculopathy data (including digital ulcers), the presence of pulmonary fibrosis, microstomia, gastroesophageal reflux and dysphagia, although these findings were not consistent between studies. Later, Morrisroe et al. found an association between PAH and digestive disorders (esophageal stenosis but not dysmotility, intestinal hypomotility, anal incontinence), joint contractures, calcinosis, digital ulcers, telangiectasias, mild ILD, dry syndrome and a greater degree of cutaneous sclerosis [34]. In contrast to those findings, we found a lower frequency of digital ulcers and esophageal involvement (globally considered) in patients with elevated esPAP compared to those with normal esPAP. However, renal crisis was more frequent in patients with elevated esPAP, whereas the prevalence of RP, liver disease and thyroid function alterations did not differ between groups. Various studies describe thyroid pathology as more common in patients with PAH than in the general population [35–37]. In our environment, thyroid alterations have been described in 51% of patients, mainly hypothyroidism (almost always subclinical) and positive anti-thyroid antibodies [38]. There is speculation around the implication of treatment with epoprostenol in the development of thyroid pathology (especially hyperthyroidism) in patients with PAH. Epoprostenol may induce hyperthyroidism via cyclic adenosine monophosphate, similar to TSH, although this mechanism would not explain more than a small group of the detected thyroid alterations [39].

Table 4 Prevalence of the different types of PH in the main published series

	Method	PH	PAH	PH-ILD	Post-PH	Other
Avouac et al.	Screening and RHC	7%	3.6%	1.9%	1.4%	PVOD 0.2%
Iudici et al.	Screening and RHC	6.5%	3.7%	1.4%	1.3%	
Morrisroe et al.	Screening and RHC	14.2%	11.8%	0.3%	1.1%	PAH on exertion 0.9%
DETECT	RHC in at-risk population	31%	19%	6%	6%	
RESCLE	RHC and clinical judgement	17.8%	3.7%	8.3%	2.8%	Unclassified PH 3%

PH pulmonary hypertension, *PAH* pulmonary arterial hypertension, *PH-ILD* pulmonary hypertension secondary to interstitial lung disease, *post-PH* postcapillary pulmonary hypertension, *RHC* right heart catheterisation, *PVOD* pulmonary veno-occlusive disease

Our work has some limitations. First, RHC was not done systematically to all patients. This is a retrospective study on data collected in a national multicentre registry of patients. Data were not collected according to a pre-established study protocol to make an exhaustive and uniform data collection, but they derive from the routine clinical practice. RHC is not usually performed to all patients with slight elevation of the esPAP in the echocardiogram if clinical PAH data are not present. Moreover, according to the current guidelines of the European Societies of Cardiology and Respiratory [1], it is not necessary to perform a RHC to patients with echocardiographic data of PH if there is evidence of left heart or respiratory disease. Thus, we have applied this diagnostic algorithm to classify some patients with elevated esPAP on the echocardiogram but without RHC as secondary PH. Second, as previously noted, the absence of the PCWP value impeded classifying the PH in 36 cases (40.9% of patients with PH confirmed via RHC). Third, regarding the investigation of risk factors, we evaluated which factors were associated with an elevated esPAP in the echocardiogram and not with confirmed PAH. It is possible that these associations were not maintained if only patients with PAH confirmed with RHC were considered. However, we believe that the associations found do not lack value.

Conclusions

In conclusion, we found a prevalence of confirmed PAH in Spanish patients with SSc lower than expected (3.7%), probably related to the small number of RHCs conducted and the lack of classification of PH confirmed via RHC in a non-negligible percentage of patients. Unlike other studies, the probability of having elevated esPAP was found to be higher in patients with dSSc compared to those with lSSc and in patients with ATA compared to those with ACA.

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Compliance with ethical standards

Disclosures None.

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