Noninvasive assessment of systolic pulmonary artery pressure in systemic lupus erythematosus: retrospective analysis of 93 patients

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Abstract

Objective

To describe the frequency of patients with an elevated systolic pulmonary artery pressure (sPAP) estimated by Doppler echocardiography in a population of SLE patients followed in a tertiary reference centre.

Methods

A search of our Internal Medicine Department database identified 93 SLE patients followed between 1995 and 2005. Their medical records were reviewed retrospectively. The PH threshold was defined as sPAP ≥35mmHg. Characteristics of PH and non-PH SLE patients were compared using Fisher's, chi-square or Wilcoxon's exact test.

Results

Elevated sPAP was detected in 12/93 (13%) patients. When analysing the mechanisms of PH, it was considered as secondary to specific lung involvement in 2 cases, due to severe left ventricular dysfunction in 1 patient and probably corresponding to SLE-associated PAH in the 9 remaining subjects. Univariate analyses showed that sPAP≥35mmHg was more common in Black subjects (50 vs. 20%, p=0.03), in patients with longer disease duration (14±8 vs. 9.5±8 years, p=0.049), and in patients with a history of peripheral nervous system involvement (25 vs. 4%, p=0.02), pericarditis (58 vs. 27%, p=0.04), anti-Sm (42 vs. 11%, p=0.01), and anticardiolipin antibodies (75 vs. 31% p=0.007).

Conclusion

PH is a relatively common complication of SLE patients managed in tertiary care centres. Doppler echocardiography allows non-invasive detection of elevated sPAP in this population that should then benefit from gold-standard techniques including right-heart catheterisation in order to confirm the diagnosis, as well as the cause and severity of PH.

Key words

pulmonary arterial hypertension, pulmonary hypertension, systemic lupus erythematosus, prognosis

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Introduction

Pulmonary hypertension (PH) is defined by means of right-heart catherisation showing an elevated mean pulmonary artery pressure ≥25mmHg at rest (1, 2). Pulmonary arterial hypertension (PAH) corresponds to precapillary PH (pulmonary capillary wedge pressure ≤15mmHg) and is a rare disease observed in 15 cases/10^6 in the general population (3). PAH can be idiopathic, familial or associated with connective tissue diseases or other conditions, like human immunodeficiency virus infection, appetite-suppressant use, congenital heart disease, and portal hypertension. More common causes of PH include systolic and diastolic left heart failure, hypoxemia and chronic respiratory diseases, and chronic thromboembolic PH (CTEPH) (4).

Among connective tissue diseases, systemic sclerosis (SSc) is the most common cause of PAH followed by systemic lupus erythematosus (SLE). In the French Registry, these conditions accounted for 76 and 15% of the cases, respectively (3). In a large multicentre study of 599 French SSc patients, a systematic screening based on clinical symptoms and Doppler echocardiography, followed by confirmation of right-heart catheterisation when PH was suspected, indicated that PAH prevalence was 8% (5). Other studies confirmed that 8 to 15% of SSc patients displayed PAH (6), emphasising the relevance of this severe complication of SSc which represents a leading cause of death in that population (7, 8). Other causes of PH were not uncommon in SSc patients, mainly left-heart diseases and hypoxia due to chronic respiratory diseases, mainly pulmonary fibrosis (5, 6), highlighting the importance of investigating properly these patients.

Similar studies have not been performed in patients displaying SLE. Therefore, the purpose of the present study was to systematically analyse the files of SLE patients followed in our department with the objective to determine the frequency and describe the characteristics of SLE-associated PH.

Patients and methods

We identified all the patients with SLE diagnosed according to the American Rheumatism Association criteria (9) entered in the computerised database of the Internal Medicine department and followed between 1995 and 2005. Patients with mixed connective tissue disease, SSc, polymyositis, dermatomyositis or rheumatoid arthritis were excluded from the study. For each patient, demographics (gender, ethnicity, age at SLE diagnosis, SLE duration at evaluation), clinical manifestations of SLE (malar rash, photosensitivity, discoid lupus, alopecia, oral/nasal ulcers, Raynaud's phenomenon, cutaneous vasculitis, arthralgias, arthritis, pericarditis, cardiac valvular involvement, lung disease, pleuritis, nephropathy, central and peripheral nervous system involvement, venous and arterial thrombosis, obstetrical events, associated antiphospholipid antibody syndrome), at time of diagnosis or during follow-up were collected, as were the main biological and immunological findings (anti-Sm, anti-cardiolipin and anti β2-GP I antibodies, lupus anticoagulant).

Patients with previously diagnosed PH were followed in the department and did not undergo further investigations. Patients who had never been evaluated for PH or who had been investigated more than 3 years earlier, systematically underwent echocardiography. The different cardiologists applied the specific methodological requirements for echocardiographic PH detection. Complete Time-Motion-bidimensional and Doppler echocardiography with standard views and procedures was performed after 20 minutes at rest, Systolic pulmonary artery pressure (sPAP) was considered equal to right ventricular systolic pressure (RVSP) in the absence of right ventricular outflow obstruction. RVSP was calculated by adding an estimation of right atrial pressure (5 to 10mmHg according to the size of the inferior *vena cava*) to the systolic right atrial-ventricular pressure gradient (PG), which was calculated using the modified Bernoulli equation, $\Delta P=4V^2$, where ΔP is the PG and V is the maximal velocity tricuspid regurgitation measured. As recommended by others, PAP was considered to be normal in patients whose Velocity Tricuspid Regur-

gitation (VTR) could not be quantified provided that the right ventricle was normal. PH was suspected when sPAP was ≥35mmHg (*i.e.* V≥2.8m/s).

Only one patient with severe symptoms underwent right heart catheterisation. PAH was confirmed when the mean PAP was ≥25mmHg, together with a capillary wedge pressure ≤15mmHg and pulmonary vascular resistance >3mmHg/L/min.

Statistical analysis

Statistical analyses were conducted using SAS software, version 8.2 (SAS Institute Inc, Cary, NC). Values are reported as numbers for categorical variables and means±standard deviation (SD) for continuous variables. Demographics, clinical manifestations of SLE and main biological and immunological findings were compared between patients with and without PH. Qualitative variables were compared using a chi-square test or, when appropriate, Fisher's exact test, and quantitative variables using Wilcoxon's test. For the survival analysis, we used the date of lupus diagnosis as the start point to determine the survival duration in each group (patients with or without PH). The cut-off date was 1 April 2010. The Kaplan-Meier method was used to estimate overall survival at each time point. Patients who were lost to follow up were considered as censored at the date of the last available visit. Survival distributions were compared using the Cox-Mantel logrank test. For all statistical analyses, a *p*-value ≤0.05 was considered significant.

Results

The characteristics of 93 patients are summarised in Table I. Fifty-nine had a recent echocardiography and 34 underwent Doppler echocardiography for the purpose of this study.

Patients with elevated echo-derived sPAP (Table II)

Systolic PAP>35mmHg was detected in 12 (13%) of the 93 SLE patients, 10 women and 2 men, half of whom were Black. The mean value of sPAP was 41±7 mmHg. One patient, patient (n.4 in Table II) underwent a right heart catheterisation that confirmed the diagnosis of PAH.

The mean age at the time of SLE diagnosis was 36±15 years and SLE had lasted a mean of 14±8 years. The mean interval between the onset of SLE and the detection of elevated sPAP was 10±2 years (0 to 25 years). SLE had been diagnosed before elevated sPAP detection in all but one patient (n.10 in Table II). Elevated sPAP was diagnosed at the time of a lupus flare for patients n.4 and n.10, but SLE was quiescent in the remaining ten. Patients n. 3, 6, 8 and 9 had cardiac valve disease, but only patient n.3 had severe left heart dysfunction that explained the elevation of sPAP. Severe parenchymal lung disease was found in patients n.1 and n.2 with irreversible airflow obstruction in the former and interstitial lung disease in the latter, both as the consequences of SLE. PH was considered to be related to left ventricular dysfunction in patient n.3 and to lung disease in patients n.1 and n.2. For the remaining nine patients, SLE-associated PAH was suspected but formally confirmed by right heart catheterisation in only one patient (n.4).

Immunosuppressants were given to patients n.4 and n.10 to treat these manifestations, associating elevated sPAP and rapid clinical impairment. Patient

Table I. Characteristics of 93 patients with systemic lupus erythematosus according to pulmonary hypertension status.

	All patients n=93	No PH group n=81	PH group n=12	*p* value[a]
Demographics				
Female, n (%)	85 (91)	75 (92)	10 (83)	NS
Ethnicity, n (%)				
White,	44 (47)	41 (51)	3 (25)	NS
Blacks (Africa and West Indies)	22 (24)	16 (20)	6 (50)	0.03
North Africa	17 (18)	14 (17)	3 (25)	NS
Others	10 (11)	10 (12)	0 (0)	NS
Age at diagnosis (mean ± SD), years	32 ± 12	31 ± 15	37 ± 15	NS
SLE duration at evaluation (mean ± SD), years	10 ± 6	9.5 ± 8	14 ± 8	0.049
Clinical, n (%)				
Malar rash	42 (45)	39 (48)	3 (25)	NS
Photosensitivity	24 (26)	23 (28)	1 (8)	NS
Discoid lupus	4 (4)	4 (5)	0 (0)	NS
Alopecia	21 (22)	18 (22)	3 (25)	NS
Oral/nasal ulcers	15 (16)	13 (16)	2 (17)	NS
Raynaud phenomenon	34 (36)	29 (36)	5 (42)	NS
Cutaneous vasculitis	14 (15)	12 (15)	2 (17)	NS
Arthralgias	87 (93)	75 (93)	12 (100)	NS
Arthritis	52 (56)	46 (57)	6 (50)	NS
Péricarditis	29 (31)	22 (27)	7 (58)	0.04
Cardiac valvular involvement	21 (22)	17 (21)	4 (33)	NS
Lung disease	7 (7)	5 (6)	2 (17)	NS
Pleuritis	15 (16)	11 (14)	4 (33)	NS
Nephropathy	34 1(36)	27 (33)	7 (58)	NS
CNS involvement	13 (14)	10 (12)	3 (25)	NS
PNS involvement	6 (6)	3 (4)	3 (25)	0.02
Venous thrombosis	24 (26)	20 (25)	4 (33)	NS
Arterial thrombosis	4 (4)	2 (2)	2 (17)	NS
Obstetrical events	8 (9)	8 (10)	0 (0)	NS
Associated APS	19 (20)	15 (18)	4 (33)	NS
Antibodies detected, n (%)				
Anti-Sm antibodies	14 (15)	9 (11)	5 (42)	0.01
Anti-cardiolipin antibodies	34 (36)	25 (31)	9 (75)	0.007
Lupus anticoagulant	12 (13)	9 (11)	3 (30)	NS
Anti β2-GP I	8 (9)	8 (12)	0 (0)	NS

APS: antiphospholipid antibody syndrome; β2-GP I: β2-glycoprotein 1; CNS: central nervous system; NS: no significant; PH: pulmonary hypertension; PNS: peripheral nervous system; SLE: systemic lupus erythematosus.

[a] Comparison of non PH versus PH patient groups.

Table II. Clinical and laboratory data for SLE patients with PH detected by Doppler-echocardiography.

Pt. n.	Gender/ Age[a] (years)	PH-SLE interval[b] (years)	Estimated sPAP (mmHg)	Type of PH	PH-related symptoms	APS	aCL	Sm	Clinical manifestations	Outcome
1	F/27	19	40	Related to lung disease	Dyspnea, chest pain	Yes	+	–	RP, PE post PH diagnosis	Alive
2	F/22	2	35	Related to lung disease	Dyspnea on exercise	No	+	+	Pericarditis, type IV GN	Dead
3	F/51	11	44	Related to left heart dysfunction	Dyspnea on exercise	No	+	–	Pericarditis, type IV GN, myocarditis	Dead
4	F/23	16	60	isolated	Dyspnea, chest pain.	Yes	+	–	RP, mononeuritis multiplex, type II GN, portal, splenic and mesenteric vein thrombosis, PE after PH diagnosis	Dead
5	F/24	14	38	isolated	None	No	+	+	Retinal and cerebral vasculitis, pericarditis, type IV GN.	Alive
6	F/26	1	37	isolated	None	No	–	+	RP, pericarditis, type IV GN, seizures, thrombotic microangiopathy.	Dead
7	F/58	9	40	isolated	None	No	+	–	Seizures.	Alive
8	M/32	25	45	isolated	None	Yes	+	–	Pericarditis, popliteal artery thrombosis, TIA, coronary artery disease.	Dead
9	M/66	9	45	isolated	None	No	–	–	None.	Dead
10	F/39	0	110	isolated	Dyspnea	Yes	+	+	RP, pericarditis, mononeuritis multiplex.	Alive
11	F/30	6	40	isolated	None	No	+	+	RP, polyneuropathy, type II GN.	Alive
12	F/28	10	35	isolated	None	No	–	–	Pericarditis, intra-alveolar hemorrhage, type III and IV GN.	Alive

aCL: anticardiolipin antibodies; APS: antiphospholipid antibody syndrome; GN: glomerulonephritis; PE: pulmonary embolism; Pt: patient; RP: Raynaud's phenomenon; sPAP: systolic pulmonary artery pressure; TIA: transient ischemic attack.
[a] Age at lupus diagnosis;
[b] Time interval between the onset of SLE and the detection of elevated sPAP.

n. 4 initially received oral corticosteroids and intravenous cyclosphosphamide pulses, and then the oral endothelin-receptor antagonist bosentan was prescribed because the response to immunosuppressant was not sufficient. Despite initial improvement on bosentan, combination therapy with the phosphodiesterase type-5 inhibitor sildenafil was prescribed later due to clinical deterioration. Unfortunately, this patient died from an unknown cause in January 2010. Patient n.10 was initially treated with cyclophosphamide pulses, oral corticosteroids and anticoagulant leading to dramatic improvement in pulmonary pressures (sPAP dropped from 110 to 35 mmHg) and clinical symptoms. She has been taking corticosteroids alone for 4 years. The other patients did not receive PAH-specific therapy. Patients n. 1, 4, 8 and 10 were given oral anticoagulants for associated antiphospholipid antibody syndrome.

Comparison of patients with and without elevated sPAP

According to our univariate analyses, a significantly higher percentage of patients with elevated sPAP were black (50% *vs*. 20%, p=0.03). They also had a significantly longer mean SLE duration (14±8 *vs*. 9.5±8 years), had more peripheral nervous system involvement (25% *vs*. 4%, p=0.02), and more pericarditis (58% *vs*. 27%, p=0.04). They also had more anti-Sm (42% *vs*. 11%, p=0.01) and anticardiolipin antibodies (75% *vs*. 31% p=0.007) (Table I).

In terms of outcome, the presence or the occurrence of PH had a negative impact on outcome (Fig. 1). Six patients with PH and 2 without PH died during the observation period. Survival rates for patients with PH were 92%, 92% and 82% at 5, 10 and 15 years, respectively, as compared with 100%, 100% and 97% for patients without PH (p=0.0002).

Discussion

Prognosis of patients with systemic lupus erythematosus has improved over the last ten years with the ability to treat disease-specific manifestations (10). Pulmonary hypertension is a rare but potentially life-threatening complication of SLE. Estimates of PH frequency in SLE patients range from 0.5 to 14%,

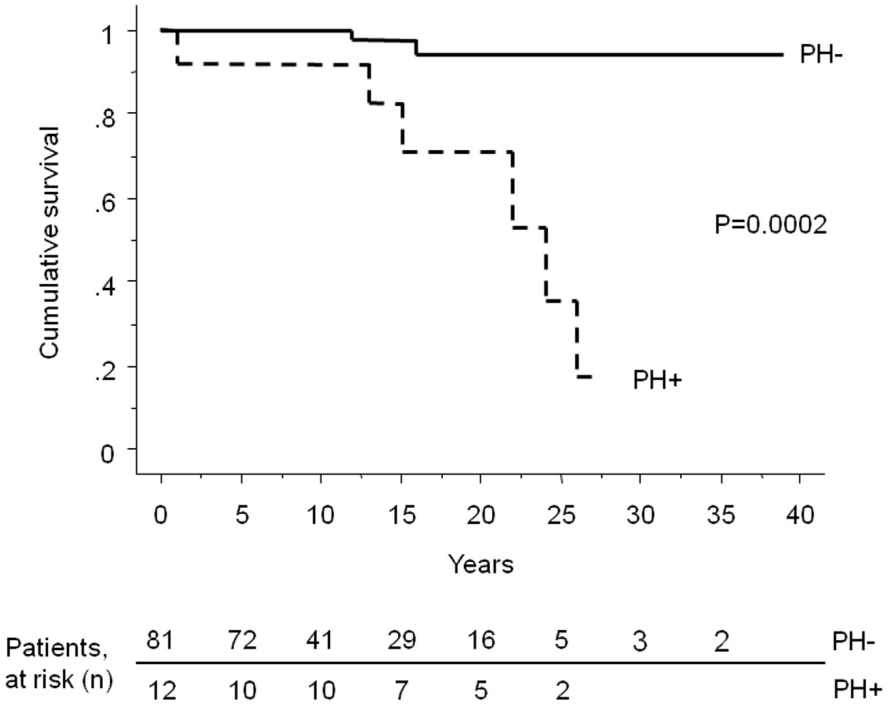

Fig. 1. Kaplan Meier survival estimates of patients with systemic lupus erythematosus according to pulmonary hypertension (PH) status.
Survival rates for patients without PH (solid line) were 100%, 100% and 97% at 5, 10 and 15 years, respectively, as compared with 92%, 92% and 82% for patients with PH (dashed line) (p=0.0002 by the Cox-Mandel log-rank test).

suggesting that this condition may be more common than previously thought (11-16). Our estimates based on echo-Doppler screening are in accordance with the main studies reported (11-16). The majority of SLE patients with PH were female (approximately 90%). Overall 3- and 5-year survival rates were 45% and 17% respectively, and prognosis was worse than for patients with idiopathic PAH (iPAH) (12). Our findings indicate that SLE patients with elevated sPAP were more frequently black patients and patients with anti-Sm antibodies, which had never been reported previously. We also observed that patients with elevated sPAP had significantly more peripheral nervous system involvement.

When focusing on PAH, the vascular changes in SLE-associated PAH are similar to those seen in iPAH, and comprise intimal hyperplasia, smooth muscle hypertrophy and medial thickening. Several pathological mechanisms have been proposed to explain PAH, including vasoconstriction, vasculitis and thrombosis (10-11). PAH is clearly associated with antiphospholipid and anticardiolipin antibodies. The very high frequency of the latter in our patients suggests that these autoantibodies might facilitate the formation of microthrombi in the pulmonary vasculature and thereby contribute to sPAP elevation, but the relationship between them and PH in SLE remains controversial. The anticardiolipin antibodies frequency in SLE-associated PAH patients varied from 22% (17), which is the usual rate in SLE, to 68% (11) which concords with our findings. Of note, none of the patients reported in our series had evidence of chronic thrombo-embolic PH based on VA/Q lung scans.

The link between SLE disease activity and the increase of sPAP is still heatedly debated. Indeed, for some authors, pulmonary hypertensive patients were more commonly in active SLE stages (15) whereas, for others, there was no difference between PH patients and non PH patients (18).

Unlike SSc, patients with SLE or other connective tissue disease-associated PAH may respond to immunosuppressive therapy. One recent, small study showed that 5 of the 12 SLE patients responded to monthly, intravenous cyclophosphamide pulse (600mg/m^2) and high dose oral corticosteroids, whereas no SSc patients responded to that regimen (19). A positive response was indicated by sustained hemodynamic improvement after ≥1 year of treatment without adjunction of other PAH-specific therapies. Similar results were reported by Jaïs and colleagues in a larger series of 23 patients focusing on SLE and mixed connective tissue disease associated PAH (20). Interestingly, patients 4 and 10 from our present series received corticosteroids and cyclophosphamide and subsequently improved, highlighting the fact that these patients may have a reversible component.

One patient also responded initially to the dual endothelin receptor antagonist bosentan. Bosentan efficacy against connective tissue disease-related PAH was recently examined in the TRUST study (21), which evaluated 53 patients with symptomatic PAH (NYHA functional class III) associated with SSc (n=42), SLE (n=5) or undifferentiated or overlapping connective tissue diseases (n=6). Bosentan led to improved or unchanged NYHA functional class at treatment weeks 16 and 48 in 94% and 85% of the patients, respectively. Only 15% of patients worsened during the study, with 92% of patients alive at 48 weeks.

Our study has several limitations. First, this analysis was retrospective and should be repeated in a prospective way. Second, it was performed in a tertiary reference centre with a higher likelihood to select the most difficult patients with severe systemic disease. Third, right heart catheterisation was not performed in most patients when echocardiography detected an elevated sPAP. Indeed, Doppler echocardiography may overestimate sPAP, as previously demonstrated in SSc (5, 6) and PH due to diastolic left heart disease may be difficult to identify in this patient population, as previously shown in SSc (5, 6). Since the completion of this analysis, prospective evaluation of sPAP always lead to right-heart catheterisation in all patients with suspected PH.

In conclusion, elevated sPAP is relatively common in SLE patients managed in

tertiary SLE centres. While Doppler echocardiography allows noninvasive detection of elevated sPAP in this population, gold-standard techniques including right-heart catheterisation should be systematically performed in order to confirm PH, determine its cause and severity, and guide management.

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