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Pulmonary hypertension in systemic lupus erythematosus

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Abstract A prospective echocardiographic and clinical study was performed on 84 Chinese patients with systemic lupus erythematosus (SLE) and 99 controls to investigate the prevalence and the mechanism of pulmonary hypertension (PH) in SLE. Comparison between Doppler estimation and catheterization measurement was made in 12 cases to validate the predictive method. Compared to normal subjects, lupus patients had significantly increased systolic pulmonary artery pressure (SPAP) (29.59±12.52 vs 19.64±5.82, $P<0.001$), mean pulmonary artery pressure (MPAP) (15.11±7.36 vs 10.21±4.72, $P<0.001$) and total pulmonary resistance (TPR) (315.85±190.65 vs 220.37±55.92, $P<0.001$). Nine of the 84 patients presented PH, defined as SPAP >30 mmHg and MPAP >20 mmHg. Pulmonary hypertensive patients had higher serum endothelin (ET) than non-pulmonary hypertensive patients, were more commonly in active stages, and presented Raynaud's phenomenon and rheumatoid factors. ET level was correlated with echocardiographic pulmonary pressure. Pulmonary hypertension commonly occurs in Chinese patients with SLE (11%), and it correlates with the lupus activity and the elevation of serum endothelin.

Key words Systemic lupus erythematosus · Pulmonary hypertension · Echocardiography · Cardiac catheterization · Endothelin

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Introduction

Pulmonary hypertension (PH) in systemic lupus erythematosus (SLE) is becoming more intriguing in recent years. The detection rate of PH is increasing owing to widespread use of more sensitive diagnostic methods. For example, none of the 138 patients reported by Harvey [1] in 1954 was noted to have PH, while in 1989, Simonson et al. [2] found by echocardiographic methods that 14% (5/36) of the patients had PH. However, the prevalence of PH in Chinese patients with SLE has not yet been reported. Patients with SLE may present PH insidiously or suddenly, with a steady downhill progression. Multiple factors have been implicated in its pathogenesis, but the underlying causes remain unknown. Despite therapy, death occurs within 2–5 years in most cases [3, 4]. Thus, early diagnosis and pathogenic investigation of PH in SLE is becoming much more important. In the present study, we use Doppler echocardiography, combined with cardiac catheterization and a clinical laboratory exam to prospectively study the prevalence and mechanism of PH in SLE.

Materials and methods

Materials

The study population consisted of 84 Chinese patients with SLE who fulfilled the revised criteria of the American Rheumatism Association [5]. They were randomly selected from our Rheumatology Clinic or had been hospitalized (1–4 patients per week) during 1996. All persons gave their informed consent prior to their inclusion in the study. They included 80 females and 4 males, with mean age of 36.82±9.18 (ranging from 14 to 63) years old, and mean disease duration of 6.01±5.91 years. A group of 99 age- and sex-matched healthy subjects (94 females and 5 males), mean age 35.74±8.08 (ranging from 20 to 67) years old, served as controls.

Echocardiography

Patients and controls underwent combined M-mode, cross-sectional and Doppler echocardiographic study using a HP SONOS 2500

ultrasound imaging system with a 2.5 MHz transducer. Standard parasternal long-axis, short-axis and apical 4-, 5- and 2-chamber views were obtained and recorded with a Panasonic AG-6200 video recorder for subsequent review and frame-by-frame analysis. Each datum was the average of more than three values in consecutive cardiac cycles and was read or measured independently by more than two observers. In the case of disagreement, the two reviewers reached a consensus by a joint review of the study. Major pulmonary artery parameters were measured as follows:

1. Systolic pulmonary artery pressure (SPAP). Doppler recordings of tricuspid regurgitation were obtained by standard methods [6–8]. The transtricuspid pressure gradient (ΔP) was approximated with the modified Bernoulli equation $\Delta P = 4V^2$. A fixed value of right atrial pressure, 10 or 15 mmHg [6] was added to ΔP to yield systolic right ventricular pressure (SRVP). SRVP was approximated to be SPAP in the absence of pulmonary stenosis.
2. Mean pulmonary artery pressure (MPAP). Optimal Doppler pulmonary flow spectral signals were obtained [9]. Pulmonary acceleration time (ACT) was measured. MPAP was calculated using Mahan's regression equation: MPAP = 79 – 0.45 × ACT [7, 10].
3. Corrected pulmonary acceleration time (ACTc). Correction for different heart rates was performed by dividing the time indexes by the square root of the cycle length (R-R interval).
4. Cardiac output (CO). End-systolic and end-diastolic left ventricular cross-sectional area and diameter were measured in parasternal short-axis view and apical four-chamber view. Stroke volume (SV) was calculated by a modified Simpson formula programmed into the system. CO was calculated by SV times heart rate.
5. Total pulmonary resistance (TPR). TPR was calculated by a standard formula [11, 12], which is TPR (dynes · s · cm^{-5}) = MPAP/CO×80.

Pulmonary hypertension was defined as SPAP >30 mmHg and MPAP >20 mmHg [13, 14]. According to this criterion, patients were subdivided into a pulmonary hypertensive group (PH) and a non-pulmonary hypertensive group (NPH).

Right heart catheterization

Twelve patients (three from the SLE group, one suffering from congenital atrial septum defect, and another eight patients with clinical indications for the installation of an artificial pacemaker) were subjected to cardiac catheterization within 24 h (three SLE patients) or 10 days of the echocardiographic studies. Right heart catheterization was accomplished with a 7F triple-lumen Swan-Ganz catheter [14]. Phasic and mean pulmonary artery pressure were recorded. CO was determined by thermodilution or the Fick (two cases) method [14]. TPR were calculated using the standard formula given above.

Serum entothelin detection by radio immunoassay (ET)

Blood samples were drawn from radial veins within 72 h of echocardiographic study. Blood (4 ml) was collected into a chilled tube containing 10% EDTA and 400 K IU/ml aprotinin, and then centrifuged at 3000 rpm for 15 min at 4 °C. Separated plasma samples were immediately stored at –70 °C until analysis. At the time of analysis, plasma samples were thawed and then centrifuged at 3000 rpm at 4 °C for 15 min. The supernatant was extracted and measured directly.

The assay was performed by a professional technician from the RIA Center without knowledge of the patients or studies. All reagents used in this study, including antibodies were provided by East Asia Immune Technological Research Institute. There is no cross-reactivity for anti-ET antibody with human α-atrial natriuretic peptide, the angiotensions or vasoactive intestinal peptide. The lower limit of detection is 2 pg/ml. The range of detection is between 5–5120 pg/ml.

Clinical and laboratory investigation

A complete medical history of the 84 patients was collected before the echocardiographic study. The disease was considered to be active if it conformed to the lupus activity criteria [15]. All patients underwent a follow-up examination within 72 h of echocardiographic study which included (1) X-ray, (2) electrocardiogram (ECG), (3) and measurement of anticardiolipin antibody by ELISA method (ACL), (4) antinuclear antibody by immunofluorescence (IFANA), (5) anti-extractable nuclear antigen (ENA), (6) anti-double stranded DNA (anti-dsDNA), (7) rheumatoid factor (RF), (8) complement C_3 (CH_{50}), (9) erythrocyte sedimentation rate (ESR), and (10) platelet aggregation test (PAT).

Statistical analysis

Data were expressed as mean ± standard deviation. Comparisons between patients and controls, PH and NPH groups, were performed using the unpaired Student's *t*-test and small-sample-corrected χ^2 analysis. Linear regression analysis was performed between echocardiographic and catheterization data and radioimmunoassay values. The student's *t*-test (paired) was used to compare the difference between echocardiographic and catheterization data. Statistical significance was assumed when *P* was less than 0.05.

Results

Among 84 patients, 52 had analyzable Doppler tricuspid regurgitation signals, while in 99 normal subjects, only 27 presented analyzable tricuspid regurgitation signals. The patients had significantly increased SPAP, MPAP, and TPR and significantly decreased ACTc, and R-R interval compared to normal. But CO was the same in all patients (Table 1). Of the 84 SLE patients, nine presented PH with

Table 1 Echocardiographic pulmonary index of SLE patients and normal subjects

			SLE Patients (n = 84)	Normal (n = 99)	P
Age	mean ± SD range	(years)	36.82 ± 9.18 (14–63)	35.74 ± 8.08 (20–67)	NS
Sex		(female : male)	80 : 4	94 : 5	NS
SPAP[a]		(mmHg)	29.596 ± 12.52	19.64 ± 5.82	<0.001
MPAP		(mmHg)	15.11 ± 7.36	10.21 ± 4.72	<0.001
CO		(l/min)	4.18 ± 1.01	4.35 ± 0.84	NS
TPR		(dynes · s · cm^{-5})	315.85 ± 190.85	220.37 ± 55.92	<0.001
ACTc		(ms)	163.84 ± 27.57	170.12 ± 12.67	<0.05
R-R		(s)	0.75 ± 0.11	0.80 ± 0.095	<0.001

[a] The number of cases in which SPAP derived from tricuspid regurgitation was 52 for SLE patients and 27 for normal controls

Table 2 Comparison of echocardiographic data between pulmonary hypertensive (PH) group and non-pulmonary hypertensive (NPH) group in patients with SLE

	SPAP[a] (mmHg)	MPAP (mmHg)	CO (l/min)	TPR (dynes · s · cm^{-5})	ACTc (ms)	R-R (s)
PH group (n = 9)	48.81±18.43	29.80±10.65	3.85±1.07	685.61±365.95	133.31±32.14	0.73±0.14
NPH group (n = 75)	25.57±5.47	13.35±4.38	4.23±0.89	276.79±71.55	169.66±17.63	0.76±0.108
P	<0.001	<0.001	NS	<0.001	<0.001	NS

[a] The number of cases in which SPAP derived from tricuspid regurgitation was 9 for the PH group and 43 for the NPH group

Table 3 Comparison between echocardiographic and catheterization data for 12 cases[a]

Diagnosis of patients	Echocardiographic data						Catheterization data			
	SPAP	MPAP	ACTc	CO	TPR	R-R	SPAP	MPAP	CO	TPR
SLE	16.86	12.25	175	4.08	240.20	0.72	19	13	4.34	239.63
SLE	19	16.7	159	3.90	342.56	0.75	17	11	4.13	214.63
SLE	20.2	14.65	166	5.29	221.34	0.74	21	13	5.43	191.53
CHD	27	16	154.6	4.98	257.03	0.82	24	18	5.32	270.68
CHD	22.3	19.75	145	4.64	340.52	0.82	30	21	4.96	338.71
CHD		38.5	113.4	5.07	607.49	0.63		26	4.86	427.98
DCM	32.5	18.4	134.7	5.80	253.79	1.00	22	12	6.89	139.33
DCM		27.7	123.7	4.30	515.35	0.85	31	25	4.62	432.90
PMS	36.2	25	101.4	3.08	649.35	1.40	23	10	3.55	225.35
PMS	16	13.7	197	3.24	339.51	0.54	19	15	4.15	289.16
HCM		16	152.8	4.39	291.57	0.84	21	16	4.25	301.18
ASD	45.5	18.25	155.9	4.86	411.52	0.75	46	21	4.08	411.76

CHD, coronary heart disease; DCM, dilated cardiomyopathy; PMS, post-myocarditis syndrome; HCM, hypertrophic cardiomyopathy; ASD, atrial septum defect

[a] The coefficient of correlation (r) between echocardiographic and catheterization data for SPAP, MPAP, CO and TPR was 0.764 (P<0.05), 0.680 (P<0.05), 0.834 (P<0.01) and 0.529 (P = 0.06), respectively

SPAP ranging from 31.2 to 90 mmHg and MPAP from 21 to 53 mmHg, respectively. Among nine patients with PH, only four presented obvious signs of PH, including loud secondary pulmonic heart sound, prominent pulmonary segment in X-ray films and enlarged right atrium and ventricle in echocardiography. The other five patients complained of dyspnea on exertion. The PH group had significantly higher pulmonary artery pressure and resistance than the NPH group (Table 2).

Comparison between echocardiographic and catheterization data for 12 cases are listed in Table 3. Of the 12 patients, nine (75%) presented tricuspid regurgitation. The echocardiographic estimations of SPAP, MPAP, CO, and TPR correlated well with the catheterization values, and there was no significant difference between them.

Clinical and laboratory data comparisons between the PH and NPH groups are listed in Table 4. The PH group had significantly higher serum ET than the NPH group, and they were more commonly in active disease stages and presented Raynaud's phenomenon and rheumatoid factors than the NPH group. The ET level of SLE patients was significantly correlated with echocardiographic SPAP and MPAP, with the coefficient of correlation (r) equal to 0.6681 and 0.7553, respectively. After exclusion of the two high points, a significant correlation still existed with r changed to 0.3413 (P<0.05) and 0.6447 (P<0.01), respectively (Fig. 1).

Table 4 Comparison of clinical and laboratory data from pulmonary hypertensive (PH) patients and non-pulmonary hypertensive (NPH) patients

	PH	NPH	P
n (%)	9 (11)	75 (89)	
Age (years)			
mean±SD	36.80±8.64	36.23±9.38	NS
range	(24~45)	(14~63)	
Sex (female:male)	9:0	71:4	NS
Duration of SLE (years)	7.466±6.58	5.721±5.88	NS
Lupus activity (%)	66.67 (6/9)	16 (12/75)	<0.01
Steroid treatment (years)	5.123±4.32	3.39±3.75	NS
Cytotoxic treatment (%)	100 (9/9)	66.67 (50/75)	NS
Clinically evident pulmonary hypertension	44.44 (4/9)	0	<0.001
Raynaud's phenomenon	77.78 (7/9)	36 (27/75)	<0.05
Interstitial lung disease (%)	33.33 (3/9)	10.67 (8/75)	NS
ACL (+) (%)	44.44 (4/9)	26.67 (20/75)	NS
IFANA (+) (%)	88.89 (8/9)	85.33 (64/75)	NS
Anti-ENA			
Anti-Sm (+) (%)	22.22 (2/9)	26.67 (20/75)	NS
Anti-RNP (+) (%)	22.22 (2/9)	26.67 (20/75)	NS
Anti-dsDNA>30 μ/ml (%)	44.44 (4/9)	29.33 (22/75)	NS
RF (+) (%)	55.56 (5/9)	18.67 (14/75)	<0.05
$C_3H_{50}\downarrow$ (%)	44.44 (4/9)	18.67 (14/75)	NS
PAT test abnormal (+) (%)	22.22 (2/9)	17.33 (13/75)	NS
ET (pg/ml)	237.63±92.94	123.06±45.30	<0.001

Anti-Sm: antibody to Smith antigen
Anti-RNP: antibody to ribonucleoprotein

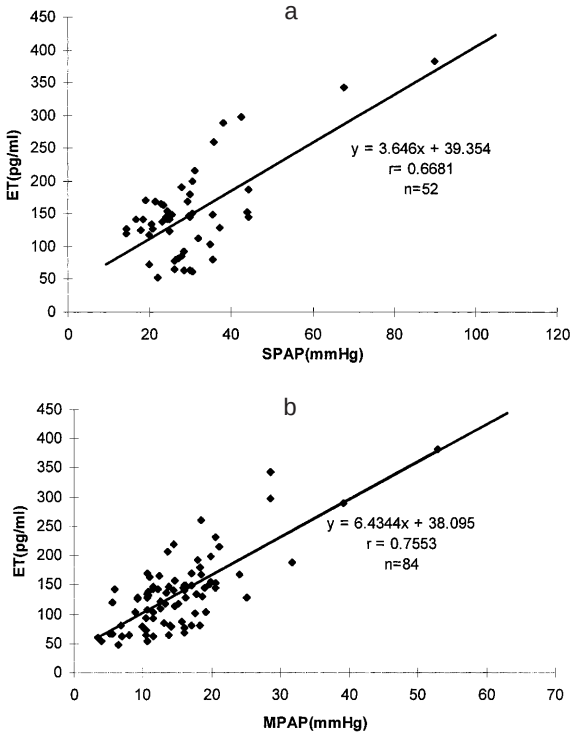

Fig. 1a, b The chart of linear regression equation between ET level and echocardiographic SPAP (**a**), and MPAP (**b**) in SLE patients. After exclusion of the two high points, the coefficients of correlation (*r*) changed to 0.3413 and 0.6447, respectively

Discussion

Pulmonary hypertension in systemic lupus erythematosus is increasingly reported in recent years. However, the prevalence was uncertain because of different methods of detection [1–3, 16–22]. In this study, we find by Doppler echocardiography that the incidence of PH in Chinese patients with SLE is 11%.

The heart rate ACTc of our lupus patients was shorter than that of normal. This led to a calculated elevation of the MPAP (= 79–0.45×ACT). For the SPAP, our study concurs with Eisenberg's [23] report that only a small number of patients with pulmonary artery pressure mildly increased at catheterization had analyzable tricuspid regurgitation signals to derive SPAP. Our detection rate of SPAP was a little higher than that of Murata's [24]. We believe that the absence of adequate velocity profiles of tricuspid regurgitation and of findings suggestive of PH by chest radiograph, ECG, or two-dimensional echocardiogram implies a normal pulmonary artery pressure, if the echocardiographic study is performed by an experienced echocardiographer using the latest equipment. However, we found a statistical significance in the comparison of SPAP between patients and controls.

After comparisons between Doppler estimations and direct measurements, we found that both the acceleration time from pulmonary flow analysis and the tricuspid regurgitation velocity were reliable predictors of pulmonary artery pressure. However, the former method was more applicable, while the latter method was more satisfactorily accurate. Using a combination of both methods for one patient, we can screen out the pulmonary hypertensive patients from a group of subjects. In present study, 5 out of 9 pulmonary hypertensive patients were subclinical. This is not surprising since it has been shown that physical or laboratory findings are often detectable only with advanced disease after a period of sustained pulmonary hypertension [25, 26]. Doppler echocardiography is sensitive in detecting early pulmonary hypertension.

To investigate the factors contributing to pulmonary hypertension, a series of clinical and laboratory examinations were carried out. The patients with higher pulmonary artery pressure had increased total pulmonary resistance but normal cardiac output. This indicated that PH was caused by morphologic and/or functional changes of the pulmonary arteries. Quismorio et al. [20] revealed that the pulmonary arteries in SLE patients with PH presented angiomatoid lesions. Moderate to marked hypertrophy of the media, and fibrosis of the subintima were frequently seen. The present study revealed that PH was highly correlated with serum ET. ET has potent, sustained vasoconstrictive and promitogenic effects in both animals and humans [27–31]. Giaid et al. [32] demonstrated ET-1 mRNA expression mostly in the endothelium of pulmonary arteries of patients with PH. We inferred that ET might similarly contribute to the pulmonary vascular abnormalities of patients with SLE, increasing pulmonary resistance and leading to PH. Yet, the precise pathophysiologic action of ET in these conditions awaits specific ET antagonists or pharmacological inhibitors for clinical use.

In the present study, PH patients were more commonly in active stages and presented rheumatoid factors and Raynaud's phenomenon. This is consistent with previous reports [2, 3, 20–22, 33]. As Quismorio et al. [20] had reported, immunoglobulin including rheumatoid factor and antinuclear antibody deposition were found in the walls of pulmonary arteries. They suggested an immune complex deposition process as a mechanism in the pathogenesis of PH in SLE. Fahey et al. [34] demonstrated that primary Raynaud's phenomenon was part of a systemic vascular response that included a decrease in size of the pulmonary capillary bed. Is it possible for us to infer that pulmonary hypertension is a kind of chronic Raynaud's phenomenon, which is characterized by recurrent vasospasms, aided by autoimmune vascular inflammation and modulated by endothelin? The precise mechanism requires further investigation.

Our study failed to follow-up all patients as was done by Winslow et al. [35], but we did observe a few cases. One patient, who was in active stage, presented a large amount of pericardial effusion, severe mitral regurgitation, and PH in echocardiography. After taking prednisone and cyclophosphamide, her SPAP dramatically dropped from about 70 mmHg to 48 mmHg and finally to under 30 mmHg, valve regurgitation resolved and pericardial effusion disappeared. Another two patients (one was not included in this study) presented obvious enlargement of

right atria and ventricules and their SPAP were equal to 78 and 90 mmHg, respectively. Prednisone and cyclophosphamide were ineffective, and prostaglandin only slightly decreased the pulmonary pressure. Both patients died shortly after treatment. These patients supported our view that PH is associated with disease activity, vasospasm and proliferative vasculitis. At first, PH is reversible and responds to high dose of steroids as the disease flare subsides. As the disease progresses, morphological changes occur in the pulmonary vessels and steady PH is established.

PH patients showed no more correlation with anticardiolipin antibody (ACL), platelet aggregative function or interstitial lung disease than patients with normal pulmonary artery pressure. This suggests that PH in our lupus patients is not likely caused by thromboembolism or loss of pulmonary vascular reserve.

In conclusion, PH, defined by SPAP exceeding 30 mmHg and MPAP exceeding 20 mmHg, occurs in 11% of Chinese patients with SLE. It is associated with lupus activity, Raynaud's phenomenon and increased serum ET, which may be of pathogenic importance.

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