

SESSION 4

VASCULAR COMPLICATIONS

S.4.1 N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE LEVELS PREDICT INCIDENT PULMONARY ARTERIAL HYPERTENSION IN SSC

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Introduction. Pulmonary arterial hypertension (PAH) is a major cause of mortality in SSC. NT-proBNP may be a useful biomarker of prevalent PAH but its role in screening for incident PAH has not been evaluated. **Methods.** Patients recruited into the Australian Scleroderma Cohort Study undergo annual echocardiography, pulmonary function tests (PFTs), 6-min walk test (6MWT) and have serum NT-proBNP measured (ElecysproBNP II). The diagnosis of PAH is based on Dana point criteria at right heart catheterization (RHC). Patients with LV dysfunction or eGFR <30 ml/min were excluded from this study. Four clinical groups were selected. Group 1 ($n=20$) had definite PAH with pre-treatment sera assayed. Group 2 ($n=30$) were considered 'at risk' for PAH based on (i) sPAP on echo >36 mmHg, (ii) FVC/DL_{CO}% >1.6 and no significant ILD, (iii) DL_{CO} <50% or (iv) resting mPAP of 20–25 mmHg at RHC. Group 3 ($n=19$) had interstitial lung disease (ILD) but no evidence of PAH on echo or RHC. Group 4 ($n=31$) were SSC patients without cardiopulmonary disease. Analysis of variance with two-group comparisons were used to determine differences in clinical characteristics and NT-proBNP level among groups. Simple and multiple linear regression were used to determine correlates of NT-proBNP. ROC curve analysis was performed to determine the optimal NT-proBNP threshold for detection of PAH.

Results. Patient characteristics are summarized in Table 1. As seen in Fig. 1, patients in Group 1 (PAH) had significantly higher mean

NT-proBNP levels than patients in Group 4 (SSc controls; $P < 0.0001$). In addition, patients in Group 2 ('at risk') had significantly higher NT-proBNP levels than those in Group 4 (SSc controls; $P = 0.008$). In simple linear regression, NT-proBNP was positively correlated with echo parameters ($P < 0.0001$). Among patients with PAH, NT-proBNP was positively correlated with mPAP on RHC (adjusted estimate = 0.048, 95% CI 0.01, 0.09, $P = 0.019$), independently of corrected DL_{CO}, FVC/DL_{CO}% ratio and 6MWD. An NT-proBNP cut-point of > 189.2 pg/ml had a likelihood ratio of 26.4 for presence of PAH (c-statistic = 0.9; sensitivity 85%; specificity 97%). An NT-proBNP level < 82.9 pg/ml had a likelihood ratio of 6.8 for exclusion of PAH (sensitivity 67.7%, specificity 90%).

Conclusions. Our findings suggest that in absence of LV dysfunction, NT-proBNP is a useful screening biomarker for PAH in SSC, with levels > 189.2 pg/ml and < 82.9 pg/ml defining patients with a high and low likelihood of PAH, respectively. Further prospective studies are required in unselected patients in order to confirm these findings.

Fig. 1 NT-proBNP level according to group.

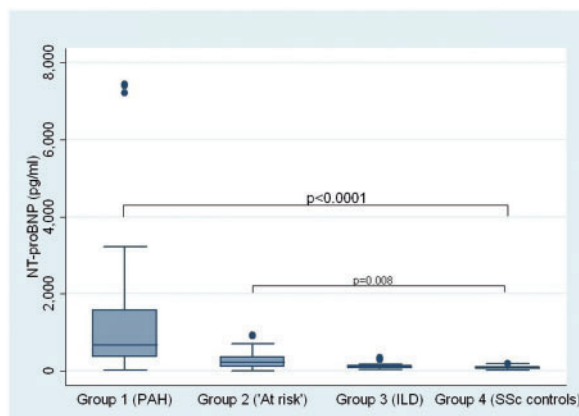


TABLE 1.

	Group 1, PAH	Group 2, at risk	Group 3, ILD	Group 4, SSc controls	P-value
Number	20	90	19	31	NA
Sex, n (%)					
Female	16 (80)	25 (83)	14 (74)	31 (100)	0.041
Male	4 (22)	5 (17)	5 (26)	0	
Disease subtype, n					
Limited	16	28	6 (3)	22	<0.0001
Diffuse	3	2	0	8	
MCTD	1	0	0	1	
Age at SSc onset, mean (s.d.), years	42 (11.4)	52 (15)	40 (16)	41 (13)	0.011
Age at time of study, mean (s.d.), years	62 (10.3)	66 (11.8)	51.1 (12.7)	48.4 (10)	<0.0001
Disease duration at study, mean (s.d.), years	20.4 (12.8)	14.5 (10.4)	10.8 (7.9)	7.6 (7.2)	0.0001
Echo parameters, mean (s.d.)					
TR velocity, ms/s	3.81 (0.69)	2.95 (0.28)	2.58 (0.38)	2.20 (0.18)	<0.0001
sPAP, mmHg	65.25 (27.82)	43.8 (7.16)	33.54 (7.73)	26.2 (2.57)	<0.0001
RHC parameters, mean (s.d.)					
mPAP, mmHg	39.50 (12.36)	NA	NA	NA	NA
mftAP, mmHg	9.94 (2.96)				
PVR	6.16 (3.10)				
6MWD, m	335 (96)	401 (114)	458 (84)	502 (74)	0.0001
WHO-FC					
I	0	5	2	22	<0.0001
II	3	10	10	4	
III	12	13	6	2	
IV	3	0	1	0	
PFT					
FVC, per cent predicted	71.6 (24.7)	100.6 (19.5)	71 (14.6)	100.9 (13.12)	<0.0001
Corr DL _{CO} %	43.5 (12.2)	59.8 (14.7)	47.4 (13.8)	87.2 (14.3)	<0.0001
fVc:DL _{CO} ratio	1.68 (0.47)	1.75 (0.46)	(0.35)	1.17 (0.19)	<0.0001
NT-ProBNP, pg/ml	1791 (2509)	278 (243)	133 (87)	75 (43)	<0.0001

S.4.2 SURVIVAL AND PROGNOSTIC FACTORS IN PATIENTS WITH INCIDENT AND NEWLY DIAGNOSED SSC-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION FROM THE FRENCH REGISTRY

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Background. Pulmonary arterial hypertension (PAH) is one of the leading causes of death in SSc. Management of patients with SSC-associated PAH (SSc-PAH) is rapidly evolving and recently reported survival is better than in historical cohorts (albeit still unsatisfactory). However, no data on incident patients are available since 2006.

Aims and objectives. This study describes the characteristics and outcome of SSc patients prospectively enrolled in the multicentre French PAH registry since 2006

Methods. SSc patients (according to American College of Rheumatology and/or LeRoy and Medsger's criteria) enrolled in the registry between January 2006 and November 2009 were prospectively included if they had a pre-capillary PAH confirmed by right heart catheterization <1 year prior to enrolment (incident patients with newly diagnosed PAH). Patients with interstitial lung disease (ILD) on high-resolution CT (HRCT) were included if forced vital capacity (FVC) >70%.

Results. A total of 100 SSc patients were included; 81% were women. Mean age at PAH diagnosis was 65 (12) years, 86% of patients had lcSSc, 80% were in New York Heart Association functional class (NYHA FC) III or IV and 15% had ILD on HRCT, mean FVC and the ratio of diffusing capacity of the lung for carbon monoxide/alveolar volume (DL_{CO}/VA) were 92 (20%) and 54 (20%) of predicted values, respectively. At baseline, mean 6-min walk distance (6MWD) was 266 (119)m and mean pulmonary vascular resistances were 674 (346) dyn.s.cm⁻⁵. Median follow-up was 2.4 years with 45 deaths observed; overall survival was 86, 72, 52 and 36% at 1, 2, 3 and 4 years, respectively. Univariate analysis identified age (HR=1.04), NYHA functional class (HR=4.03), desaturation after 6-min walk test (HR=0.90), DL_{CO}/VA (HR=0.98), presence of an ILD (HR=2.63) and cardiac index (HR=0.53) as factors prognostic of survival. Other parameters did not reach statistical significance ($P < 0.05$), including SSc subtype and mPAP.

Conclusions. These results confirm the poor prognosis for incident and newly diagnosed SSc-PAH patients even in the modern era of treatment. NYHA functional class, age and presence of an ILD at the diagnosis of PAH were important prognosis factors. Poor right ventricular haemodynamic function and desaturation during the 6-min walk test were also associated with mortality. As 80% of patients are still diagnosed with an NYHA function Class III/IV which appears as one of the most important prognosis factor, screening allowing an earlier diagnosis should be a priority.

S.4.3 CLINICAL ASSOCIATIONS OF PULMONARY HYPERTENSION IN EARLY SSC: A REPORT FROM THE EULAR SCLERODERMA TRIALS AND RESEARCH GROUP (EUSTAR) DATABASE

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Background. Pulmonary hypertension (PH) in SSc may have different causes, the most common being pulmonary arterial hypertension (PAH), PH secondary to interstitial lung disease and PH secondary to left ventricular (LV) dysfunction. Although in most patients PH is diagnosed late in the disease course, development of all types of PH has been also described in early patients. The EUSTAR database allows us to analyse the clinical associations of PH, in a large number of early SSc patients.

Objective. To identify the clinical associations of PH detected by echocardiography (PH-echo), in a large group of recently diagnosed SSc patients.

Patients and methods. EUSTAR collects prospectively the Minimal Essential Data Set (MEDS), on all sequential patients fulfilling the ACR diagnostic criteria in participating centres. Patients with disease duration of <3 years at the first EUSTAR entry were selected, and only baseline data from the first visit were analysed. Binary logistic regression, chi-square and t -test were used to analyse differences between groups with or without PH-echo.

Results. From 1072 patients (19% men), 482 had diffuse and 590 had limited disease. Mean age at entry was 53 (14) years, and at first non-Raynaud symptom 51 (16) years. Mean disease duration was 18 (6) months and time between the onset of Raynaud and first non-Raynaud symptom was 3 (7) months. PH-echo was present in 184 (18%) patients. PH was highly associated ($P < 0.0001$ for all) with older age, lung involvement (lung fibrosis, restriction, low DL_{CO}), cardiac involvement (cardiac blocks, LV systolic and diastolic dysfunction) and very active disease (EUSTAR activity index, acute-phase response, ischaemic ulcers, joint contractures, muscular atrophy, high mRSS). To a lesser extent is also associated with renal involvement (renal crisis $P=0.01$; high blood pressure $P=0.05$; proteinuria $P < 0.0001$). The results are similar when the subgroups of diffuse disease, limited disease, males, females or patients with disease duration <1 year were analysed.

Conclusions. In early SSc patients, PH-echo is present in patients with very active disease, showing cardiac, lung and renal involvement. Although some of these patients might present true PAH, others may have PH secondary to lung or left heart involvement. Since treatment for PH of different causes is not the same, our findings emphasize the need to perform right heart catheterization to clearly diagnose the cause of PH in every SSc patient.

S.4.4 PULMONARY HYPERTENSION ASSESSMENT AND RECOGNITION OF OUTCOMES IN SCLERODERMA (PHAROS): PREDICTIVE FACTORS IN THE DEVELOPMENT OF PULMONARY HYPERTENSION IN A HIGH-RISK POPULATION WITH SSc

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Introduction. The PHAROS registry is a prospective observational longitudinal cohort study, designed to understand the natural history of pulmonary hypertension (PH) in SSc.

Method. Pre-PH is defined by one of the following entry criteria: echocardiogram systolic pulmonary arterial pressure (sPAP) of >40 mmHg or diffusion lung capacity of carbon monoxide (DL_{CO}) <55% predicted or the ratio of per cent forced vital capacity (FVC) / %DL_{CO} >1.6. Patients were followed biannually. Right heart catheterization (RHC) was performed if PH was suspected, and confirmed if the mean pulmonary arterial pressure (mPAP) ≥25 mmHg. Descriptive statistics and Kaplan-Meier estimate of the time to PH diagnosis were performed.

Results. There were 246 pre-PH subjects enrolled between May 2005 and August 2011. Patients were followed for a mean of 2.5 (1.2) years. Thirty-two subjects developed PH confirmed during follow up. Based on WHO classification at Dana Point, 19 were classified as WHO Group 1 PAH and 13 as WHO Groups 2 and 3 PH. Fig. 1 shows the time to PH was 11% at 2 years, 15% at 3 years and 30% at 4 years. There were no statistically significant demographic features in the 32 PH⁺ subjects compared with the Non-PH group (Table 1). At baseline, the PH⁺ group had a significantly lower 6-min walk distance and significantly more exercise-induced hypoxia than the non-PH group. The PH⁺ group had lower entry %DL_{CO} and higher FVC%/DL_{CO} %, though this did not reach statistical significance.

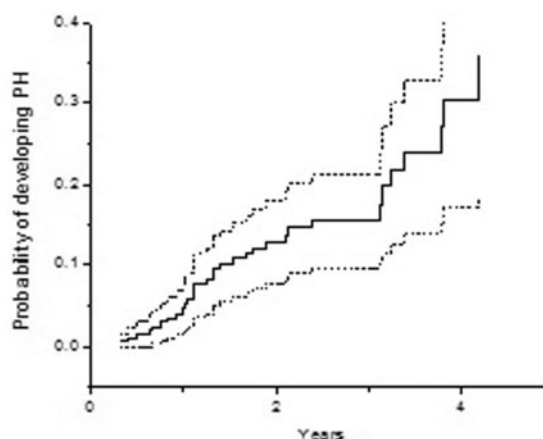
The mean echo sPAP at entry in the PH⁺ group was significantly higher (OR=2.37, 95% CI 1.1, 5.1), and subsequently increased to 54.1 (18.0) mmHg, leading to RHC. Thirteen of these patients [whose mean echo sPAP was 47 (10.3) mmHg] had an initial normal RHC [mPAP 21.2 (2.8) mm Hg], but subsequently developed PH. Overall, 66 of the 246 patients had a normal RHC; their mean echo sPAP was 40 (11.3) mmHg which was significantly higher than the RHC sPAP [30.2 (5.6) mmHg, $P < 0.001$].

Conclusion. PH was confirmed in 13% of these high-risk patients, with 30% developing PH 4 years after entry. Exercise hypoxia and an entry echo sPAP >40 were strongly associated with future PH. However, frequent false elevations in echo sPAP required an RHC to confirm PH.

TABLE 1. Entry characteristics of Non-PH and PH⁺ patients

	Non-PH (n = 214)	PH ⁺ (n = 32)	P-value
Mean age at entry, years	56.2 (11.2)	59.3 (9.0)	0.08
Gender, female, n (%)	186 (87.3)	27 (84.4)	0.86
Race, Caucasian, n (%)	156 (73.2)	21 (65.6)	0.62
Mean time from onset of Raynaud's, years	11.5 (11.6)	11.9 (10.2)	0.84
Mean time from onset of non-Raynaud's, years	10.1 (10.9)	10.0 (8.6)	0.9
SSc subtype, limited, n (%)	133 (65.2)	20 (62.5)	0.91
Antibody, n (%)	(n = 185)	(n = 31)	
ACA	46 (24.9)	9 (29.0)	0.65
Anti-Scl70	34 (18.4)	2 (2.5)	0.12
Isolated nucleolar pattern	28 (15.1)	9 (29.0)	0.07
Mean walk distance, m	418.1 (121.8)	352.3 (153)	0.03*
Oxygen saturation -92% with exercise, n/N (%)	31/132 (23.5)	14/25 (56)	0.002*
	(n = 209)	(n = 31)	
Mean %DL _{CO}	51.2 (18.6)	46.4 (17.3)	0.18
Mean FVC%/DL _{CO} %	1.78 (0.59)	2.0 (1.11)	0.19
Patients meeting PFT criteria at entry, n/N (%)	128/209 (61.2)	25/31 (80.6)	0.06
	(n = 200)	(n = 31)	
Mean echo sPAP, mmHg	38.3 (8.8)	44.3 (9.7)	0.001*
Patients meeting echo criteria at entry, n (%)	62 (31.0)	16(51.6)	0.04*

Fig. 1 Probability of developing PH vs years in study (n = 218, with 95% CI). X-axis: years in the study; Y-axis: probability of developing PAH/PH.



SESSION 5

THE HEART

S.5.1 CLINICAL AND ECHOCARDIOGRAPHIC CORRELATIONS OF EXERCISE-INDUCED PULMONARY HYPERTENSION IN SSc: A MULTICENTRE STUDY

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Background. Patients with SSc are at risk of developing pulmonary hypertension (PH), which is associated with a poor prognosis. Exercise-Doppler echocardiography (EDE) enables identification of exercise-induced increase in pulmonary artery systolic pressure (PASP) and may provide a thorough non-invasive haemodynamic evaluation.

Aim. To evaluate the clinical and echocardiographic determinants of exercise-induced increase in PASP, assessed by EDE, in a large population of SSc patients.

Methods. We selected 164 SSc patients [age 58 (13) years, 91% females] with normal resting PASP (<40 mmHg), who underwent a comprehensive 2D and Doppler echocardiography, and a graded bicycle semi-supine EDE. Pulmonary vascular resistances (PVRs) were estimated non-invasively from tricuspid regurgitant maximal velocity and right ventricular outflow tract time-velocity integral. A cut-off value of PASP ≥50 mmHg and PVR ≥3.0 Wood Units (WUs) at peak exercise was considered as indicative of significant exercise-induced increase in PASP and PVR, respectively.

Results. Sixty-nine (42%) patients showed a significant exercise-induced increase in PASP. Among them, peak PVR ≥3 WU were present only in 11% of patients, which is ~5% of the total population. Univariate analysis showed that age, presence of interstitial lung disease (ILD) and both right and left diastolic dysfunction are

predictors of peak PASP ≥50 mmHg, but none of these parameters predict elevated peak PVR.

Conclusions. Exercise-induced increase in PASP occurs in almost one-half of SSc patients with normal resting PASP. Peak exercise PASP is affected by age, ILD and right and left ventricular diastolic dysfunction, and only in 5% of the patients is associated to an increase in PVR during exercise, suggesting heterogeneity of the mechanisms underlying exercise-induced PH in SSc.

Fig. 1

