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 (ElecsysproBNP 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 pretreatment sera assayed. Group 2 (n = 30) were considered ‘at risk’ for PAH based on (i) sPAP on echo >36 mmHg, (ii) FVC/DLCO% >1.6 and no significant ILD, (iii) DLCO <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 = 0.006). 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 Dlco, FVC/Dlco% 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 = 0.8; 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.](image)
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 (DLCO/VA) were 92 (20%) and 54 (20%) of predicted values, respectively. At baseline, mean 6-min walk distance (6MWMD) was 286 (119) 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, 56 and 32% 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), DLCO/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, were square–ant i–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 mean pulmonary arterial pressure (mPAP) >40 mmHg or diffusion lung capacity for carbon monoxide (DLCO) <55% predicted or the ratio of per cent forced vital capacity (FVC) / %DLCO >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 %DLCO and higher FVC%/DLCO %, 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.
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.